10/507,510

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/28829 A2

(51) International Patent Classification[7]: C07D 207/00

(21) International Application Number: PCT/US01/29926

(22) International Filing Date: 24 September 2001 (24.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/234,967 25 September 2000 (25.09.2000) US
09/761,850 18 January 2001 (18.01.2001) US

(71) Applicant: QUESTCOR PHARMACEUTICALS, INC. [US/US]; 3260 Whipple Road, Union City, CA 94587-1217 (US).

(72) Inventors: CHONG, Lee; 37469 Marsten Drive, Nemark, CA 94560 (US). FRECHETTE, Roger; 40 Estate Lane, Reading, MA 01867 (US). SCOTT, Carole; 6593 Flanders Drive, Newark, CA 94560 (US). TESTER, Richard; 877 Heatherstone Way, Mountain View, CA 94040 (US). SMITH, Whitney; 1122 Richmond Street, El Cerrito, CA 94530 (US). CHIBA, Katsumi; Enoki 33-94 Suita, Osaka 564-0053 (JP). SAKAMOTO, Masatoshi; 2-11-6-706 Miyahara Yodogawa, Osaka 532-0003 (JP). GLUCHOWSKI, Charles; 154 Coolspring Court, Danville, CA 94506 (US).

(74) Agents: POISSANT, Brian, M. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/28829 A2

(54) Title: PEPTIDE DEFORMYLASE INHIBITORS

(57) Abstract: The invention is directed to a novel class of compounds, which inhibits peptide deformylase, pharmaceutical compositions containing compounds that inhibit peptide deformylase, and method of treating various infections.

PEPTIDE DEFORMYLASE INHIBITORS

1. FIELD OF THE INVENTION

The present invention relates to a novel class of compounds, which inhibit peptide deformylase, pharmaceutical compositions containing compounds that inhibit peptide deformylase, and methods of treating various infections.

2. BACKGROUND OF THE INVENTION

One of the most grave problems facing mankind is the continual battle against infectious diseases. Infectious diseases are the leading cause of death worldwide and the third leading cause of death in the United States. A particularly troublesome trend that has emerged in recent years is that infectious diseases that were once susceptible to treatment with antibiotics are now becoming resistant to those antibiotics. Consider, for example, the bacterium *Staphylococcus aureus*, the most common cause of hospital-acquired infection. The discovery that penicillin killed bacteria led to the common use of penicillin during World War II in army hospitals. Soon after the debut of penicillin, strains of *Staphylococcus aureus* were isolated that were resistant to penicillin. In fact, these resistant strains were commonly found in hospitals where penicillin was heavily used. The chemically modified penicillin derivative methicillin was developed and found to be effective against penicillin resistant strains, but incredibly, soon after the introduction of methicillin, new methicillin resistant strains were isolated. Currently, many methicillin resistant *Staphylococcus aureus* strains have been characterized and are causing significant issues both within and outside the hospital setting. It appears that the capability of bacteria to become resistant to drugs is weakening our ability to fight bacterial infections.

New antibiotics are desperately needed as clinically significant bacterial pathogens have acquired resistance to nearly all existing antibiotics (Chopra et al., 1997, *Antimicrob. Agents Chemother.*, 37:1563-1571; Cohen, 1992, *Science*, 257:1050-1055; Kunin, 1993, *Ann. Intern. Med.*, 118:557-561; Neu, 1992, *Science*, 257:1064-1073; Tenover and Hughes, 1996, *JAMA*, 275:300-304).

Bacteria acquire resistance to antimicrobial drugs through a remarkable variety of mechanisms (Russell and Chopra, 1996, Understanding antibacterial action and resistance, 2nd ed. Ellis Horwood, New York, NY; Jacobs, 1994, *Clin. Infect. Dis.*, 19:1-10; Hooper and Wolfson, 1993, *Am. Soc. Microbiol.*, 1993:97-118). The robust fitness of microorganisms is a manifestation of their short replication times and their ability to evolve

in the face of the selective pressure exerted by antibiotics. In order to survive, microorganisms have developed the ability to adapt quickly and effectively to changes in the environment such as changes in the light intensity, oxygen levels, acidity and exposure to antibiotics. The emergence and spread of resistant bacteria is primarily caused by acquisition of drug resistance genes resulting in a broad spectrum of antibiotic resistance (*e.g.*, extended-spectrum cephalosporin-resistant mutant beta-lactamases found in several bacterial organisms). Genetic exchange of multiple-resistance genes, by transformation, transduction and conjugation, combined with selective pressures in settings such as hospitals where there is heavy use of antibiotic therapies, has enhanced the survival and proliferation of antimicrobial agent-resistant bacterial strains occurring by, *e.g.*, spontaneous mutations. *Id.* Resistance has inevitably developed to all antimicrobial agents, although the extent to which bacteria develop resistance to antimicrobial drugs and the speed with which they do so varies with type. (Gold and Moellering, Jr., 1996, *New Eng. J. Med.*, 335(19):1445-1453). Prevention of life threatening microbial infections coupled with medical practice aimed at minimizing the development of drug resistance are certainly important (Moellering, 1990, *Scand. J. Infect. Dis., Suppl.* 70:18-24; McCaig and Hughes, 1995, *JAMA* 273:214-219; Guillemot, 1998, *JAMA*, 279:365-370), but to effectively battle infectious diseases, it is necessary to develop new antimicrobial drugs.

The biochemical apparatus for the synthesis of polypeptides in bacteria and eukaryotes is strikingly different. It is preferable to have antimicrobial drugs that disrupt bacterial metabolism but that do not interfere with the host's metabolism. Antimicrobial drugs that interfere with the biochemical machinery of the host may cause the deleterious side effects associated with certain drugs. Thus, there is a need for antimicrobial drugs that specifically inhibit bacterial metabolism while not effecting eukaryotic biochemistry.

A significant difference between bacterial and eukaryotic protein synthesis is the use of formylated methionine as the first amino acid used during ribosome based synthesis of polypeptides. In most cases eukaryotic protein biosynthesis is initiated with methionine whereas bacterial biosynthesis commences with N-formyl methionine. Proper protein folding and function in bacteria usually occurs only after the N-formyl group is removed from the nascent polypeptide chain. This is accomplished by an enzyme called peptide deformylase (PDF).

A variety of hydroxamic acid derivatives have been previously disclosed. One of the first examples discovered was actinonin. After the discovery of actinonin, and the deconstruction that these types of compounds inhibit bacterial growth it was found that they inhibit matrix metalloproteases. For relevant literature see *e.g.*, *J. Chem Soc. Perk. Tran.*

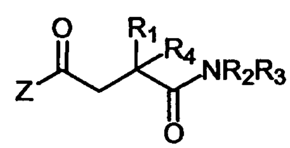
1(9) 819-860, WO 98/18754, WO 99/57097, US Patent Nos. 5,712,300, 4,325,964, 4,225,617.

WO 99/59568 describes methods of using certain hydroxamic acid derivatives for antibacterial compositions. Large genera of compounds are disclosed yet only a few examples are given and the biological activities are not reported. It is not even know if the compounds disclosed therein are selective inhibitors of peptide deformylase.

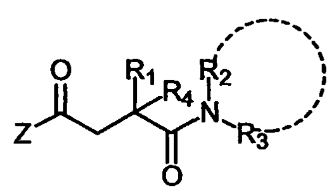
There is a need to develop new antimicrobial drugs in view of the capability of microbes to develop resistance to existing drugs; in particular there is a need for drugs that specifically affect the micro-organisms and not the host. The present invention is meant to address these and other needs.

3. SUMMARY OF THE INVENTION

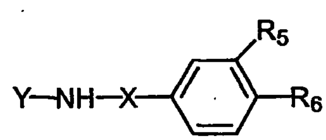
The present invention relates to compounds represented by formulas I-IV:



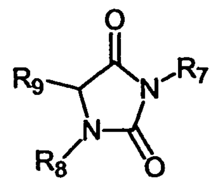
Formula I



Formula II



Formula III



Formula IV

or a pharmaceutically acceptable salt of such compounds, wherein:

Z is NHOH or OR_a wherein R_a is H, alkyl or a biocleavable moiety;

X is C=O or O=S=O;

Y is heteroalkyl, heterocyclic, or substituted derivatives thereof;

R_1 is C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof;

R_2 and R_3 together with nitrogen represent a 4, 5, 6, or 7 membered heterocyclic ring optionally substituted with one of the following substituents -OH, $-CH_2OH$, -O-C(=O)-heterocyclic, -O-C(=O)-NH-aryl, -NH-C(=O)-aryl, -C(=O)-N(C_2-C_6 alkyl)$_2$, -NH-(C_1-C_6 alkyl)-heterocyclic, -NH-C(=O)-NH-alkyl, -NH-C(=O)-NH-aryl, -NH-C(=O)-NH-heterocyclic; or

R_2 and R_4 together with nitrogen form a ring through a $-CH_2$-CH_2- linkage wherein R_3 is H, C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof; or R_2 is methyl;

R_3, as defined above forms a ring with R_2, or represents H, or is alkyl, heteroalkyl, aryl, heterocyclic, and substituted derivatives thereof;

R_3 when not in a ring with R_2 is alkyl, heteroalkyl, aryl, heterocyclic, and substituted derivatives thereof;

R_4 when not in a ring with R_2 is H, C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof; or is together with R_2 and nitrogen as defined above to form a ring through a $-CH_2$-CH_2- linkage;

R_5 is -H, $-NO_2$, $-NH_2$, -NH-C(=O)-H, -NH-C(=O)-CH_3, -NH-S(O_2)-CH_3, $-CH_2$-NH-alkyl, $-CH_2$-NH-heteroalkyl, $-CH_2$-NH-heterocycyl, or substituted derivatives thereof;

R_6 is -H, $-NO_2$, $-NH_2$, -NH-C(=O)-H, -NH-C(=O)-CH_3, -NH-S(O_2)-CH_3, $-CH_2$-NH-alkyl, $-CH_2$-NH-heteroalkyl, $-CH_2$-NH-heterocycyl, or substituted derivatives thereof;

R_7 or R_8 is -CHR_{10}-C(=O)-NH-OH; R_7 or R_8 when not -CHR-C(=O)-NH-OH is alkyl, heteroalkyl, heterocycyl, alkylaryl, alkylheterocyclic, or substituted derivatives thereof;

R_9 is H, alkyl, heteroalkyl, heterocycyl, alkylaryl, alkylheterocyclic, or substituted derivatives thereof; and,

R_{10} is H, alkyl, heteroalkyl, heterocycyl, alkylaryl, alkylheterocyclic, or substituted derivatives thereof.

In an embodiment of the invention antimicrobial drugs that are selective inhibitors of peptide deformylase are used to treat infection while reducing or avoiding deleterious side effects associated with therapeutic drugs that affect the host's biochemistry. In a preferred embodiment antimicrobial drugs of the invention are selective for peptide deformylase over other related enzymes such as angiotensin converting enzyme (ACE) thermolysin, collagenase and carboxypeptidase. Such selectivity minimizes the opportunity of adverse events associated with imbalances of these enzymes in the homostasis of tissue and organ functions affected by these metalloproteases.

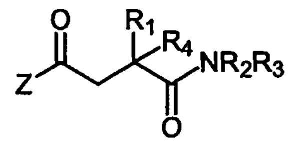
A preferred embodiment of the invention involves the use of compounds or compositions of the invention therapeutically or prophylactically against bacteria that are resistant to other antibiotics such as β-lactam, quinolone and vancomycin resistant bacteria.

In another embodiment, compounds of the invention may be used to treat contaminated or infected items, such as crops, wood, metal or plastic and the like, by methods such as, but not limited to, spraying or dusting of that agent onto the contaminated item, or impregnating that agent into the item.

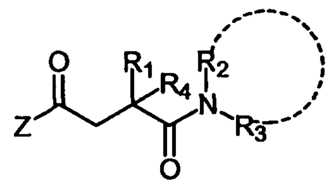
Additionally, the invention includes pharmaceutical compositions and therapies comprising a compound of the invention and a second antibacterial compound including antibiotics of the following groups consisting of, but not limited to, aminoglycosides, amphenicols, ansamycins, beta-lactams, cephalosporins, cephamycins, monolactams, oxacephems, penicillins, lincosamides, macrolides, polypeptide antibiotics, tetracyclines, 2,4-diaminopyrimidines, nitrofurans, quinolones, streptogramins, sulfonamides, sulfones, oxazolidinones and glycylcyclines.

4. DETAILED DESCRIPTION OF THE INVENTION

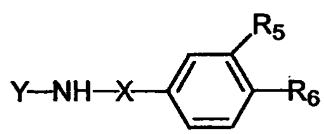
The present invention relates to compounds represented by formulas I-IV:



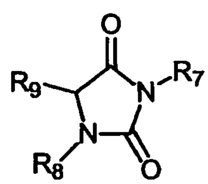
Formula I



Formula II



Formula III



Formula IV

, or a pharmaceutically acceptable salt of such compounds, wherein:

Z is NHOH or OR_a wherein R_a is H, alkyl or a biocleavable moiety;

X is C=O or O=S=O;

Y is heteroalkyl, heterocyclic, or substituted derivatives thereof;

R_1 is C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof;

R_2 and R_3 together with nitrogen represent a 4, 5, 6, or 7 membered heterocyclic ring optionally substituted with one of the following substituents -OH, $-CH_2OH$, -O-C(=O)-heterocyclic, -O-C(=O)-NH-aryl, -NH-C(=O)-aryl, -C(=O)-N(C_2-C_6 alkyl$)_2$, -NH-(C_1-C_6 alkyl)-heterocyclic,

-NH-C(=O)-NH-alkyl, -NH-C(=O)-NH-aryl, -NH-C(=O)-NH-heterocyclic; or

R_2 and R_4 together with nitrogen form a ring through a $-CH_2-CH_2-$ linkage wherein R_3 is H, C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof; or R_2 is methyl;

R_3, as defined above forms a ring with R_2, or represents H, or is alkyl, heteroalkyl, aryl, heterocyclic, and substituted derivatives thereof;

R_3 when not in a ring with R_2 is alkyl, heteroalkyl, aryl, heterocyclic, and substituted derivatives thereof;

R_4 when not in a ring with R_2 is H, C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof; or is together with R_2 as defined above to form a ring through a $-CH_2-CH_2-$ linkage.

R_5 is -H, $-NO_2$, $-NH_2$, -NH-C(=O)-H, $-NH-C(=O)-CH_3$, $-NH-S(O_2)-CH_3$, $-CH_2$-NH-alkyl, $-CH_2$-NH-heteroalkyl, CH_2-NH-heterocycyl, or substituted derivatives thereof;

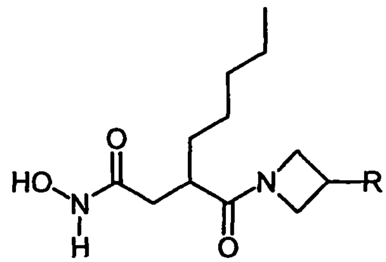
R_6 is -H, $-NO_2$, $-NH_2$, -NH-C(=O)-H, $-NH-C(=O)-CH_3$, $-NH-S(O_2)-CH_3$, $-CH_2$-NH-alkyl, $-CH_2$-NH-heteroalkyl, $-CH_2$-NH-heterocycyl, or substituted derivatives thereof;

R_7 or R_8 is $-CHR_{10}$-C(=O)-NH-OH; R_7 or R_8 when not -CHR-C(=O)-NH-OH is alkyl, heteroalkyl, heterocyclic, alkylaryl, alkylheterocyclic, or substituted derivatives thereof;

R_9 is H, alkyl, heteroalkyl, heterocycyl, alkylaryl, alkylheterocyclic, or substituted derivatives thereof; and,

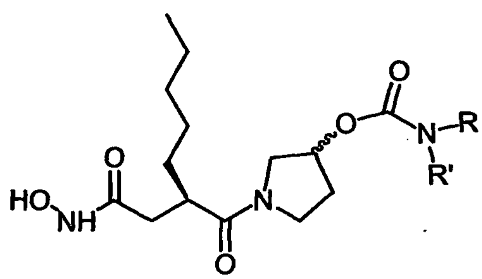
R_{10} is H, alkyl, heteroalkyl, heterocycle, alkylaryl, alkylheterocyclic, or substituted derivatives thereof.

A subset of preferred compounds encompassed by Formula I and II is defined wherein R_2 and R_3 together with the nitrogen form a 4 membered azetidinyl ring through a $-CH_2-CH_2-CH_2-$ linkage which is optionally substituted with one of the following substituents: -OH, $-CH_2OH$, -O-C(=O)-heterocyclic, -O-C(=O)-NH-aryl, -NH-C(=O)-aryl, -C(=O)-N(C_2-C_6 alkyl$)_2$, -NH-(C_1-C_6 alkyl)-heterocyclic, -NH-C(=O)-NH-alkyl, -NH-C(=O)-NH-aryl, -NH-C(=O)-NH-heterocyclic. Compounds of this subset may be represented Formula V.

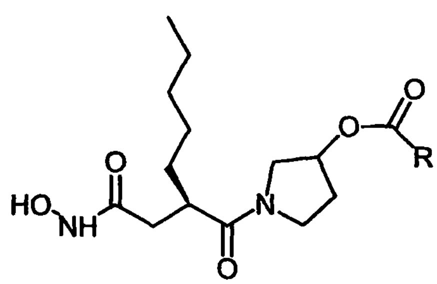


Formula V

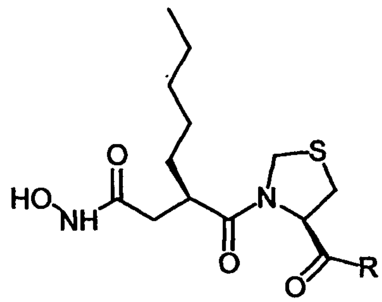
A subset of preferred compounds encompassed by Formulas I and II is defined wherein R_2 and R_3 together with the nitrogen form a five membered pyrrolidinyl ring through a $-CH_2-CH_2-CH_2-CH_2-$ linkage or a five membered thioproline ring through a $-CH_2-CH_2-S-CH_2-$ linkage which is optionally substituted with one of the following substituents: OH, CH_2OH, -O-C(=O)-heterocyclic, -O-C(=O)-NH-aryl, -NH-C(=O)-aryl, -C(=O)-N(C_1-C_6 alkyl)$_2$, -C(=O)-NH-(C_1-C_6 alkyl), -C(=O)-heterocyclic, -NH-(C_1-C_6 alkyl)-heterocyclic, -NH-C(=O)-NH-alkyl, -NH-C(=O)-NH-aryl, -NH-C(=O)-NH-heterocyclic. Compounds of this subset may be represented by Formulas VI, VII, VIII, and IX.



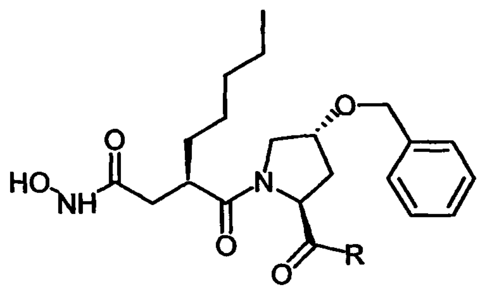
Formula VI



Formula VII

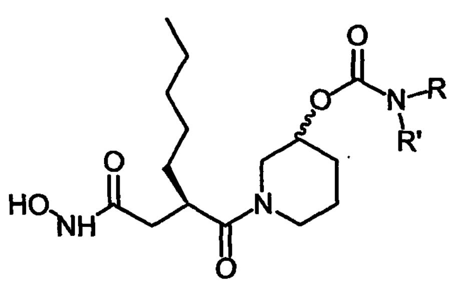


Formula VIII

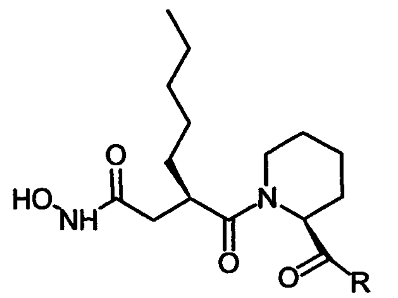


Formula IX

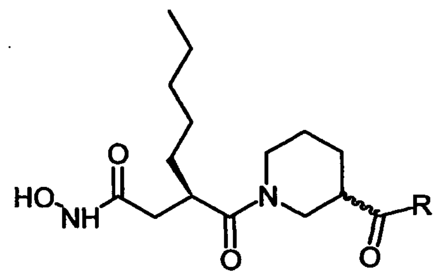
A subset of preferred compounds encompassed by Formulas I and II is defined wherein R_2 and R_3 together with the nitrogen form a six membered piperidinyl ring through a $-CH_2-CH_2-CH_2-CH_2-CH_2-$ linkage which is optionally substituted with one of the following substituents: -OH, $-CH_2OH$, -O-C(=O)-heterocyclic, -O-C(=O)-NH-aryl, -NH-C(=O)-aryl, -C(=O)-N(C_2-C_6 alkyl)$_2$, -NH-(C_1-C_6 alkyl)-heterocyclic. Compounds of this subset may be represented Formulas X, XI, XII, and XIII.



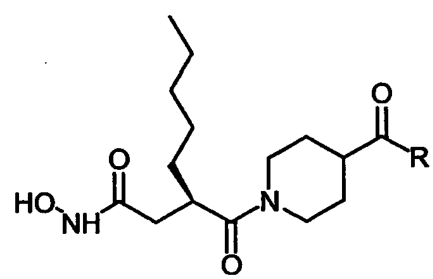
Formula X



Formula XI

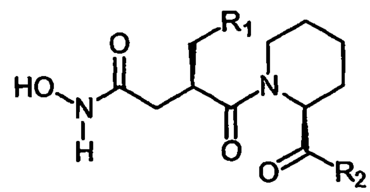


Formula XII



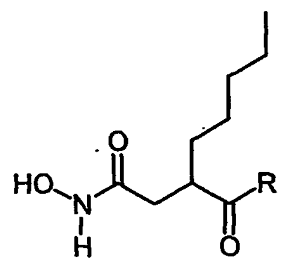
Formula XIII

A subset of preferred compounds encompassed by Formulas I and II is defined wherein R_1 is selected from the group consisting of 3,4-difluorophenyl, phenyl and cyclohexyl; and, R_2 and R_3 together with the nitrogen form a six membered piperidinyl ring through a $-CH_2-CH_2-CH_2-CH_2-CH_2-$ linkage which is optionally substituted with one of the following substituents: -OH, $-CH_2OH$, -O-C(=O)-heterocyclic, -O-C(=O)-NH-aryl, -NH-C(=O)-aryl, -C(=O)-N(C_2-C_6 alkyl)$_2$, -NH-(C_1-C_6 alkyl)-heterocyclic, -NH-C(=O)-NH-alkyl, -NH-C(=O)-NH-aryl, -NH-C(=O)-NH-heterocyclic. Compounds of this subset may be represented by Formula XIV.



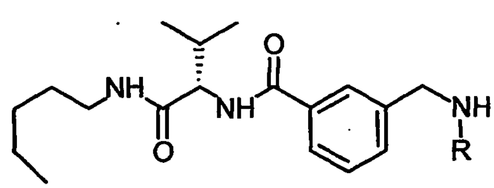
Formula XIV

A subset of preferred compounds encompassed by Formula I is defined in Formula XV wherein R is selected from the group consisting of alkyl, heteroalkyl, aryl, heterocyclic, -NH-C(=O)-NH-alkyl, -NH-C(=O)-NH-aryl, -NH-C(=O)-NH-heterocyclic, and substituted derivatives thereof. Compounds of this set may be represented by Formula XV.

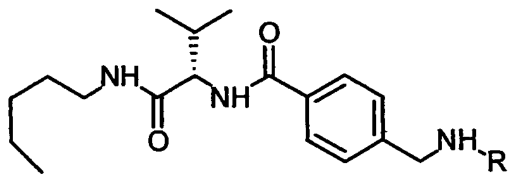


Formula XV

A subset of preferred compounds encompassed by Formula III is defined by Formulas XVI and XVII wherein R is selected from the group consisting of alkyl, heteroalkyl, aryl, heterocyclic, and substituted derivatives thereof. Compounds of this subset may be represented by Formulas XVI and XVII.

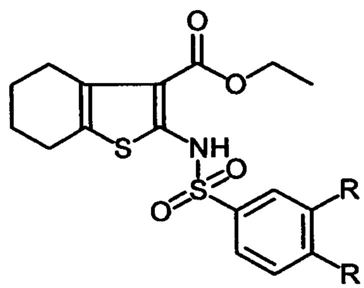


Formula XVI



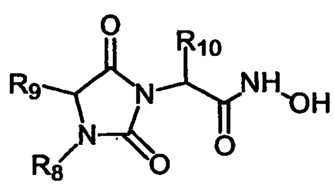
Formula XVII

A subset of preferred compounds encompassed by Formula III is defined by Formula XVIII wherein R is selected from the group consisting of -H, $-NO_2$, $-NH_2$, -NH-(C=O)-CH_3, -NH-SO_2-CH_3, alkyl, and heteroalkyl. Compounds of this subset may be represented by Formula XVIII.

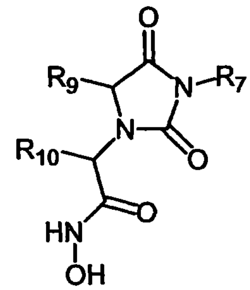


Formula XVIII

A subset of preferred compounds encompassed by Formula IV is defined by Formulas XIX and XX wherein R_7, R_8, R_9, and R_{10} are selected from the group consisting of -H, $-NO_2$, $-NH_2$, -NH-(C=O)-CH_3, -NH-SO_2-CH_3, alkyl, heteroalkyl, aryl, heterocycyl, and alkylaryl. Compounds of this subset may be represented by Formula XIX.

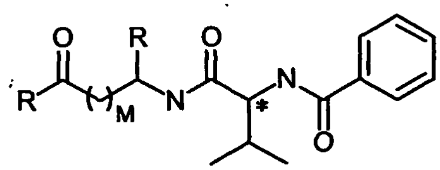


Formula XIX



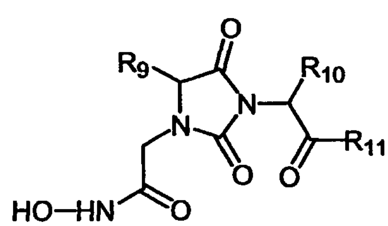
Formula XX

A subset of preferred compounds encompassed by Formula III is defined by Formula XXI, wherein M is 0 or 1, R is alkyl, the stereochemistry at the center indicated with * is R, or S, and Z is OH or NH-OH.



Formula XXI

A subset of preferred compounds encompassed by Formula IV is defined by Formula XXII, wherein R_9 is selected from the group consisting of H, alkyl, heteroalkyl, aryl, heterocycyl, and alkylaryl; R_{10} is selected from the group consisting of H, alkyl, heteroalkyl, aryl, heterocycle, and alkylaryl; and R_{11} is selected from the group consisting of H, alkyl, heteroalkyl, aryl, heterocycle, and alkylaryl.



Formula XXII

Definitions

Throughout the instant application the following terms are defined below unless otherwise stated.

As used herein the terms "alkyl" means a straight or branched chain alkyl moiety including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, and isohexyl.

As used herein the term "alkenyl" means a straight or branched chain hydrocarbon moiety having one or more double bonds including, but not limited to, propene, 1-butene, 2-butene, iso-butene, 1-pentene, 2-pentene, iso-pentene, 1-hexene, 2-hexene, and 3-hexene.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having one or more fused ring systems with from 3-12 carbons including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

As used herein the term "heteroalkyl" means an optionally substituted alkyl chain containing one or more heteroatoms or their oxidized forms selected from nitrogen, sulfur, oxygen, or phosphorous.

As used herein the terms "heterocycle" or "heterocyclic", means a 5 to 7 member ring, either aromatic or non-aromatic, containing one or more heteroatoms selected from nitrogen, sulfur, and oxygen, and optionally substituted or fused to a benzene ring system examples, include but are not limited to, thiazolyl, imidazolyl, oxazolyl, indoyl, morpholinyl, pyridinyl, pyrrilidinyl, pyrimidinyl, thienyl, furyl, piperidinyl, and piperazinyl.

As used herein the term "aryl" refers to aromatic rings and substituted derivatives thereof including, but not limited to, phenyl and fused ring systems like napthyl.

As used herein the terms "biolabile" or "biocleavable" moiety refers to a pharmaceutically acceptable, biologically degradable moiety or derivative of a compound of the invention, that is a prodrug which, upon administration to an animal or human being, is converted in the body to a compound of the invention. Such biolabile or biocleavable moieties are particularly advantageous in providing compounds of the invention that are suitable for oral administration. The suitability of any particular biolabile or biocleavable group can be assessed by conventional *in vivo* animal or *in vitro* enzyme hydrolysis studies.

It should be recognized that there are several actual or potential chiral centers in the compounds according to the invention due to the presence of asymmetric carbons. A chiral carbon within a compound gives rise to stereoisomers with R or S stereochemistry at each chiral center. The invention includes all such isomers, stereoisomers, diastereomers, enantiomers, and all racemic or optically pure forms of the compounds.

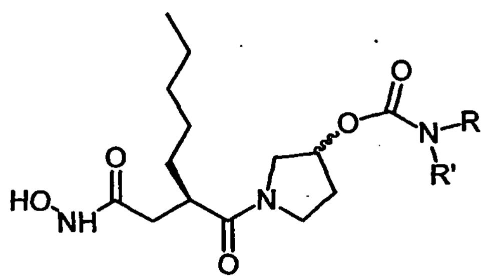
One of ordinary skill in the art of organic or medicinal chemistry will know how to resolve racemic compounds or to otherwise purify a desired stereoisomer using chiral techniques or separations.

Because of possible discrepancies in using chemical nomenclature where structures are provided for compounds or moieties the structure controls the definition of the compound or moiety, and not the chemical name.

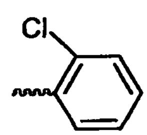
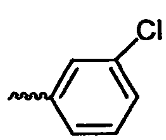
Representative examples of the compounds of formula I are shown below in Tables 1-13, these examples are not meant to be limiting but are for illustrative purposes: the IC_{50} data is the concentration (nanomolar) of the compound that inhibits E coli peptide deformylase at 50%, and the MIC data refers to the concentration of compound in micrograms per milliliters to achieve an inhibition of growth of a test organism such as E. coli.

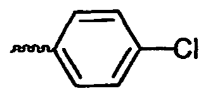
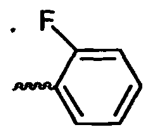
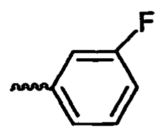
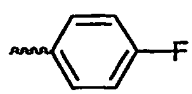
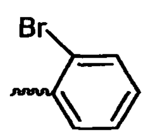
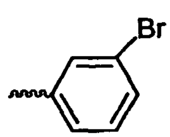
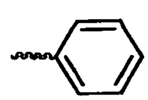
Table 1

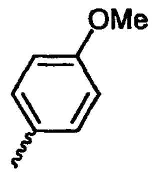
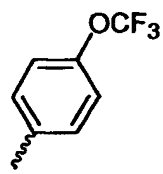
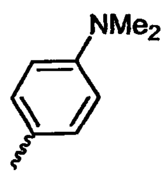
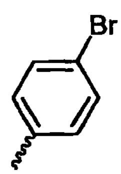
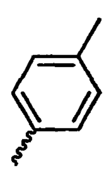
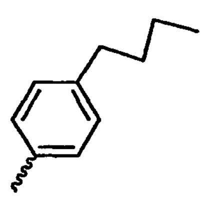
Pyrrolidine Carbamate Series I

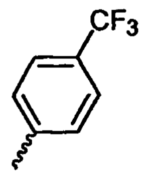
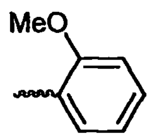
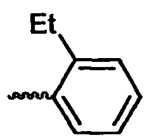
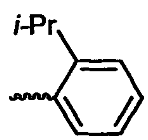
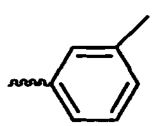
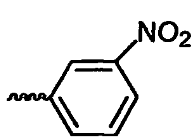


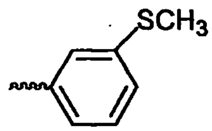
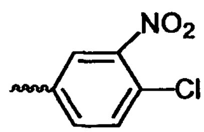
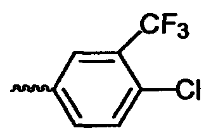
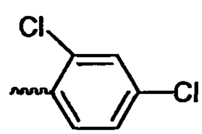
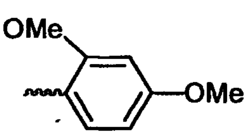
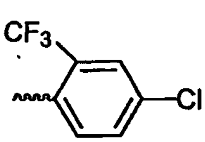
Formula VI

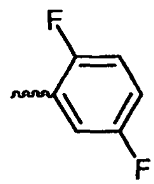
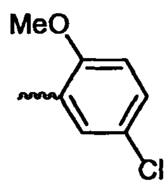
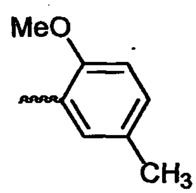
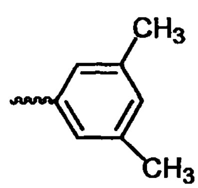
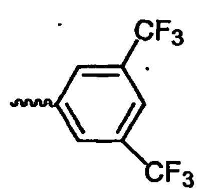
Cmpd. No.	R	R'	IC_{50}(nM)	MIC (μg/ml)
1	 2-Chlorophenyl	H	17	12.5
2	 3-Chlorophenyl	H	14	50

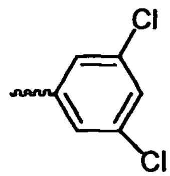
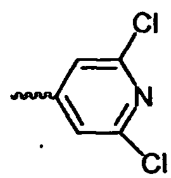
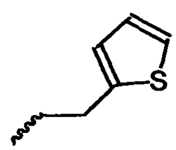
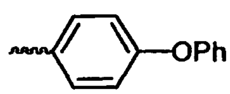
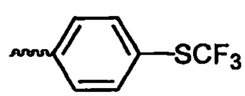
Cmpd. No.	R	R'	IC_{50}(nM)	MIC (μg/ml)
3	 4-Chlorophenyl	H	16	50
4	 2-Fluorophenyl	H	13	25
5	 3-Fluorophenyl	H	21	25
6	 4-Fluorophenyl	H	21	12.5
7	 2-Bromophenyl	H	32	25
8	 3-Bromophenyl	H	22	25
9	 Phenyl	H	19	25

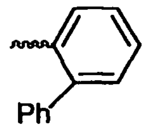
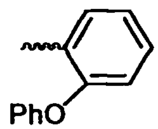
Cmpd. No.	R	R'	IC_{50}(nM)	MIC (μg/ml)
10	 4-Methoxyphenyl	H	9	25
11	 4-Trifluoromethoxyphenyl	H	40	50
12	 4- (N,N-Dimethyl-amino)phenyl	H	21	25
13	 4-Bromophenyl	H	33	50
14	 4-Methylphenyl	H	31	25
15	 4-*n*-Butylphenyl	H	160	25

Cmpd. No.	R	R'	IC_{50}(nM)	MIC (μg/ml)
16	 4-Trifluoromethylphenyl	H	25	>100
17	 2-Methoxyphenyl	H	27	25
18	 2-Ethylphenyl	H	28	12.5
19	 2-*i*-Propylphenyl	H	32	12.5
20	 3-Methylphenyl	H	17	12.5
21	 3-Nitrophenyl	H	25	25

Cmpd. No.	R	R'	IC_{50}(nM)	MIC (μg/ml)
22	 3-Methylmercaptophenyl	H	27	25
23	 4-Chloro-3-nitrophenyl	H	37	12.5
24	 4-Chloro-3-trifluoromethyl-phenyl	H	103	25
25	 2,4-Dichlorophenyl	H	65	25
26	 2,4-Dimethoxyphenyl	H	16	12.5
27	 4-Chloro-2-trifluoromethyl-phenyl	H	54	50

Cmpd. No.	R	R'	IC_{50}(nM)	MIC (μg/ml)
28	 2-5-Difluorophenyl	H	10	25
29	 2-Methoxy-5-chlorophenyl	H	38	25
30	 2-Methoxy-5-methylphenyl	H	26	25
31	 3,5-Dimethyl-phenyl	H	129	100
32	 3,5-bis-(Trifluoromethyl)phenyl	H	350	50

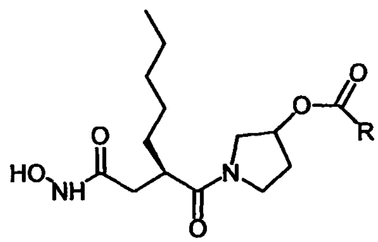
Cmpd. No.	R	R'	IC$_{50}$(nM)	MIC (μg/ml)
33	 3,5-Dichlorophenyl	H	226	50
34	 4-(2,6-Dichloropyridyl)	H	26	100
35	*n*-Pr *n*-Propyl	H	19	12.5
36	benzyl Benzyl	H	5	——
37	 2-(Ethyl-2-thiophene)	H	29	12.5
38	 4-Phenoxyphenyl	H	39	25
39	 4-Trifluoromethanemercapto-phenyl	H	37	25

Cmpd. No.	R	R'	IC_{50}(nM)	MIC (μg/ml)
40	 2-Phenylphenyl	H	43	25
41	 2-Phenoxyphenyl	H	54	25

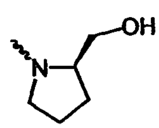
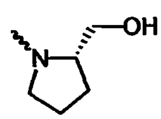
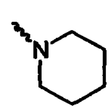
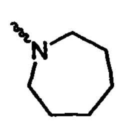
*Although the stereochemistry at the 3-position of the pyrrolidine ring is not specified, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers or with the desired stereochemical orientation, *i.e.*, the substantially or isolated *R* or *S* enantiomer.

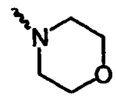
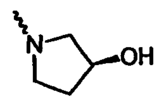
Table 2

Pyrrolidine Carbamate Series II



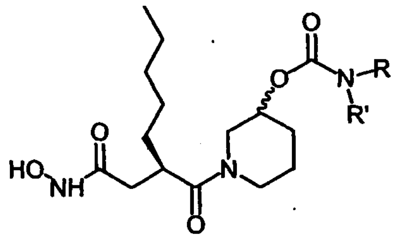
Formula VII

Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
42	 N-Pyrrolidine	11	6
43	 N-Pyrrolidine-2 (R) -methanol	14	50
44	 N-Pyrrolidine-2 (S) -methanol	5	100
45	 *N*-Piperidine	8	6.25
46	 N-Homo-Piperidine	11	3.13

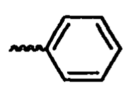
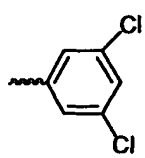
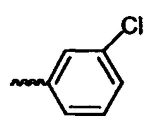
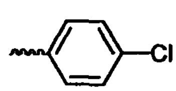
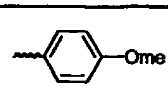
Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
47	 *N*-Morpholine	15	-----
48	 *N*-3*S*-Pyrrolidinol	30	100

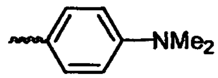
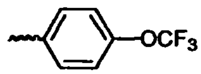
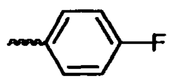
*Although the stereochemistry at the 3-position of the pyrrolidine ring is not specified, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers or with the desired stereochemical orientation, *i.e.*, the substantially or isolated *R* or *S* enantiomer.

Table 3
Piperidine Carbamate Series



Formula X

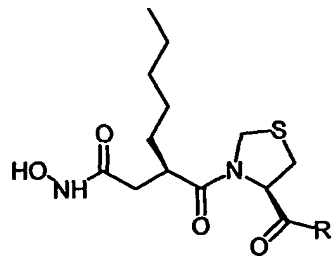
Cmpd. No.	R	R'	IC_{50} (nM)	MIC (μg/ml)
49	 - Phenyl	H	90	50
50	 3,5-Dichlorophenyl	H	200	25
51	 3-Chlorophenyl	H	176	50
52	 4-Chlorophenyl	H	147	50
53	 4-Methoxyphenyl	H	51	25

Cmpd. No.	R	R'	IC_{50} (nM)	MIC (μg/ml)
54	 4-(N,N-Dimethylamino)phenyl	H	103	25
55	 4-Trifluoromethoxyphenyl	H	78	50
56	 4-Fluorophenyl	H	350	25

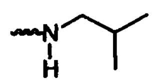
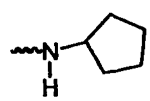
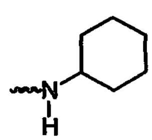
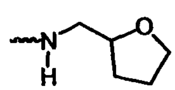
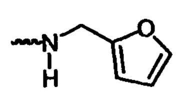
*Although the stereochemistry at the 3-position of the piperidine ring is not specified, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers or with the desired stereochemical orientation, *i.e.*, the substantially or isolated *R* or *S* enantiomer.

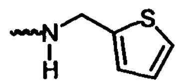
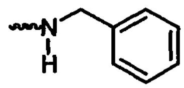
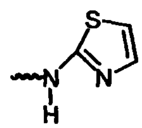
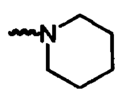
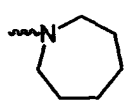
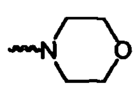
Table 4

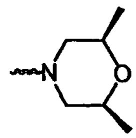
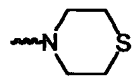
Thioproline Series



Formula VIII

Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
57	 Isobutylamino	20	3.13
58	 Cyclopentylamino	12	1.56
59	 Cyclohexylamino	15	1.56
60	 Tetrahydrofurfurylamino	14	3.13
61	 Furfurylamino	17	1.56

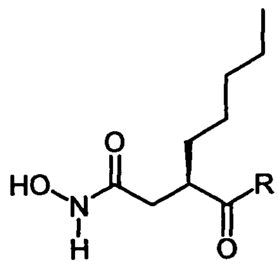
Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
62	 2-Thienylmethylamino	13	1.56
63	 Benzylamino	26	1.56
64	 2-Thiazolylamino	7	0.78
65	 Dimethylamino	26	3.13
66	 1-Pyrrolidinyl	37	1.56
67	 Piperidino	37	1.56
68	 Homopiperidino	47	6.25
69	 Morpholino	24	3.13

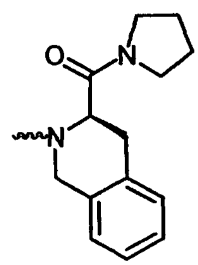
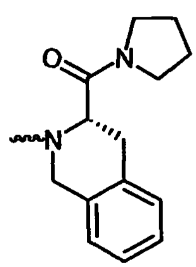
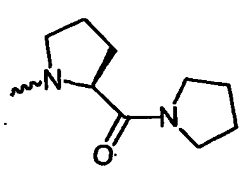
Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
70	 2,6-Dimethylmorpholino	21	6.25
71	 Thiomorpholino	25	3.13

*Although the stereochemistry at the 4-position of the thioproline ring is specified as the S enantiomer, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers, or with the *R* stereochemical orientation.

Table 5

Tic and Pyrrolidine Series



Cmpd. No.	R	IC_{50} (nM)
72	 N–1,2,3,4-Tetrahydronathyl-1-amine 2-pyrrolidinamide	22
73	 N–1,2,3,4-Tetrahydronathyl-1-amine 2-pyrrolidinamide	31
74	 N-Pyrrolidine 2-pyrrolidinamide	82, MIC=3.13 (μg/ml)

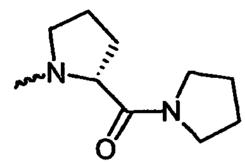
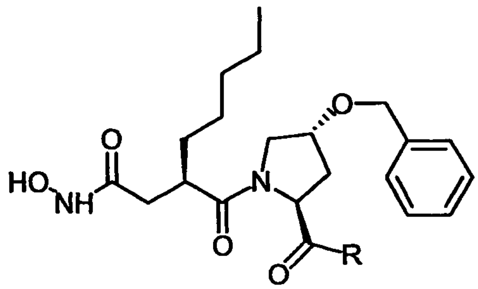
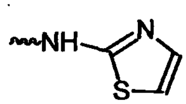
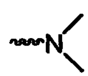
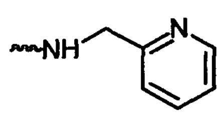
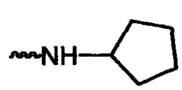
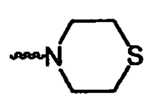
Cmpd. No.	R	IC_{50} (nM)
75	 Pyrrolidine 2-pyrrolidinamide	960

Table 6

Benzyloxyproline Series



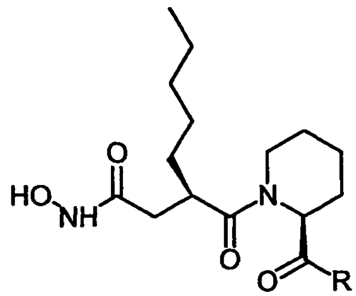
Formula IX

Cmpd No.	R	IC$_{50}$(nM)
76	 2-Thiazolylamino	8
77	 Dimethylamino	57
78	 N-2-Methylpyridyl	40
79	 N-Cyclopentylamine	20
80	 N-Thiomorpholine	65

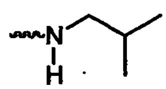
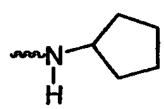
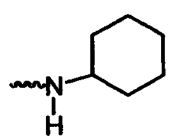
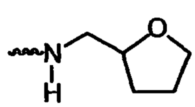
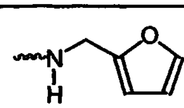
*Although the stereochemistry at the 2-position of the piperadine ring is specified, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers or with the desired stereochemical orientation, *i.e.*, the substantially or isolated *R* or *S* enantiomer.

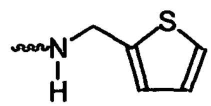
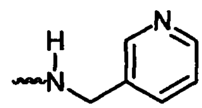
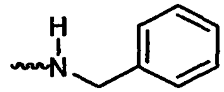
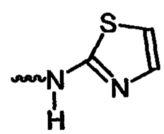
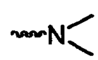
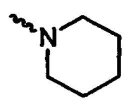
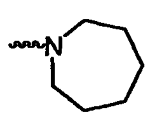
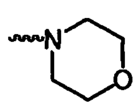
Table 7

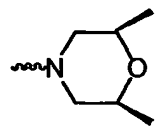
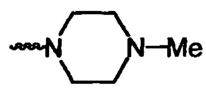
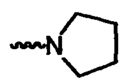
Homoproline Series I



Formula X

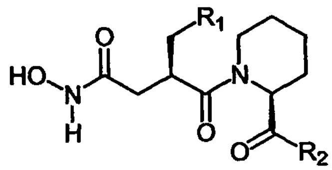
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
81	 Isobutylamino	13	12.5
82	 Cyclopentylamino	13	12.5
83	 Cyclohexylamino	13	12.5
84	 Tetrahydrofurfurylamino	11	6.25
85	 Furfurylamino	9	6.25

86	 2-Thienylmethylamino	15	6.25
87	 *N*-methyl-3-pyridyl	18	6.25
88	 Benzylamino	20	6.25
89	 2-Thiazolylamino	3	0.78
90	 Dimethylamino	17	1.56
91	 Piperidino	15	1.56
92	 Homopiperidino	16	3.13
93	 Morpholino	19	3.13

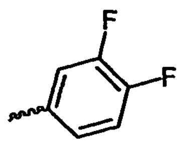
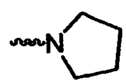
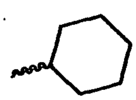
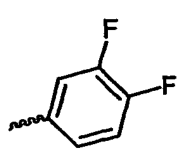
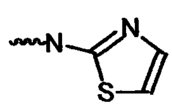
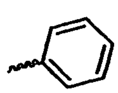
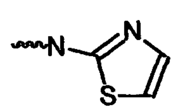
94	 2,6-Dimethylmorpholino	19	3.13
95	 Thiomorpholino	17	1.56
96	 *N*-Methyl-N-piperazine	19	6.25
97	 1-Pyrrolidinyl	13	1.56

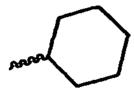
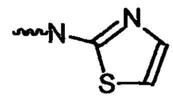
*Although the stereochemistry at the 2-position of the piperidine ring specified is as the S enantiomer, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers or as the *R* enantiomer.

Table 8
Homoproline II series



Formula XIV

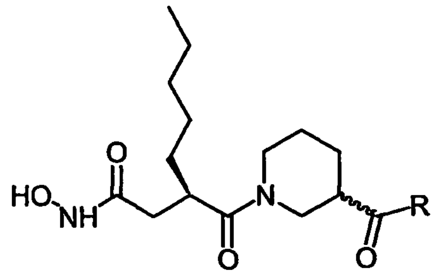
Cmpd No.	R_1	R_2	IC_{50} (nM)
98	 3,4-Difluorophenyl	 1-Pyrrolidinyl	116
99	 Phenyl	 1-Pyrrolidinyl	22
100	 Cyclohexyl	 1-Pyrrolidinyl	9
101	 3,4-Difluorophenyl	 2-Thiazolylamino	81
102	 Phenyl	 2-Thiazolylamino	25

103	 Cyclohexyl	 2-Thiazolylamino	2 .

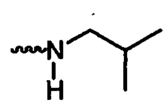
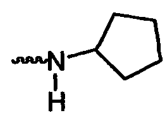
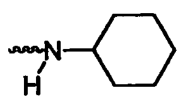
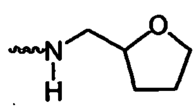
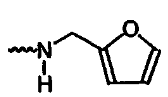
*Although the stereochemistry at the 2-position of the piperidine ring is specified, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers or with the desired stereochemical orientation, *i.e.*, the substantially or isolated *R* or *S* enantiomer.

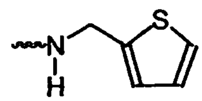
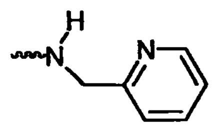
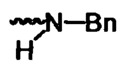
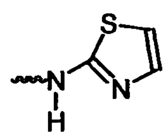
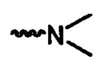
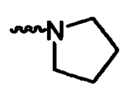
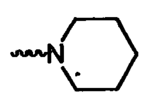
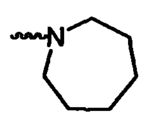
Table 9

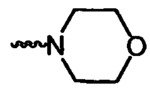
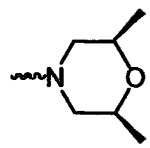
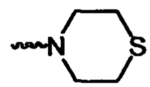
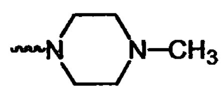
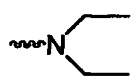
Nipecotic Acid Series



Formula XII

Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
104	 Isobutylamino	96	50
105	 Cyclopentylamino	62	50
106	 Cyclohexylamino	38	25
107	 Tetrahydrofurfurylamino	41	——
108	 Furfurylamino	150	50

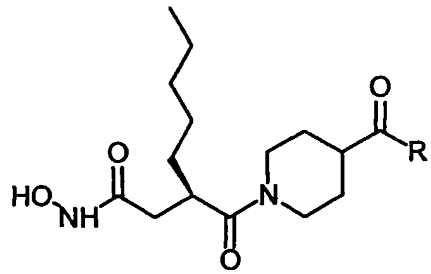
Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
109	 Thienylmethylamino	30	6.25
110	 *N*-2-Methylpyridyl	26	—
111	 Benzylamino	25	6.25
112	 2-Thiazolylamino	116	100
113	 Dimethylamino	31	50
114	 Pyrrolidinyl	40	—
115	 Piperidino	112	50
116	 Homopiperidino	44	100

Cmpd. No.	R	IC_{50} (nM)	MIC (μg/ml)
117	 Morpholino	45	100
118	 2,6-Dimethylmorpholino	49	100
119	 Thiomorpholino	205	6.25
120	 *N*-Methyl-N-piperazine	67	—
120A	 Diethylamino	50	—

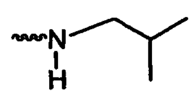
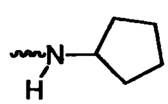
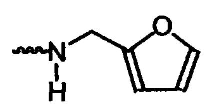
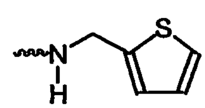
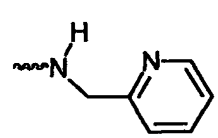
*Although the stereochemistry at the 3-position of the piperidine ring is not specified, one of ordinary skill in the art would readily recognize that the stereocenter may be generated in racemic form, *i.e.*, a mixture of *R* and *S* enantiomers or with the desired stereochemical orientation, *i.e.*, the substantially or isolated *R* or *S* enantiomer.

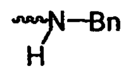
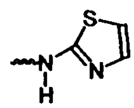
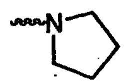
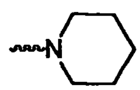
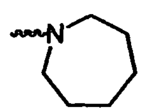
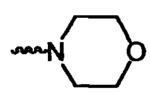
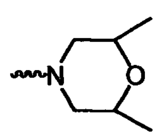
Table 10

Isonipecotic Acid Series



Formula XIII

Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
123	 Isobutylamino	48	50
124	 Cyclopentylamino	81	25
125	 Furfurylamino	44	100
126	 2-Thienylmethylamino	129	25
127	 *N*-2-methylpyridyl	34	50

Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
128	 N-Benzyl	48	50
129	 2-Thiazolylamino	29	——
130	 Dimethylamino	109	——
131	 1-Pyrrolidinyl	135	——
132	 Piperidino	318	100
133	 Homopiperidino	85	——
134	 Morpholino	83	——
135	 2,6-Dimethylmorpholino	74	——

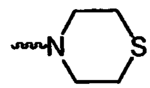
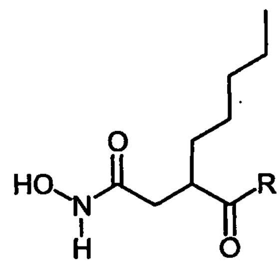
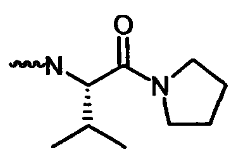
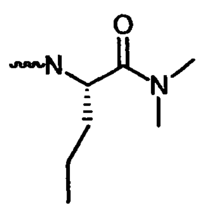
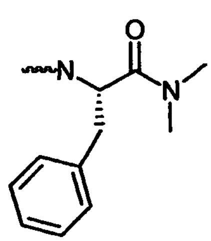
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
136	 Thiomorpholino	72	——

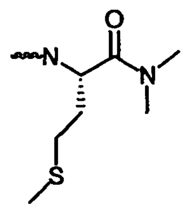
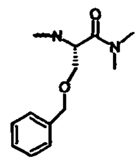
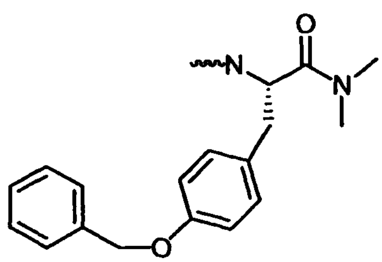
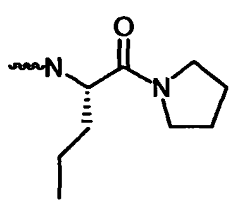
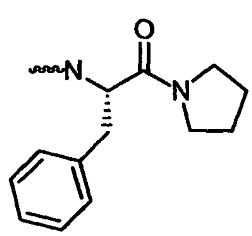
Table 11

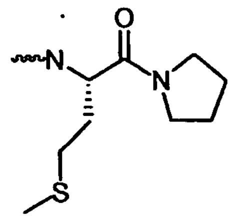
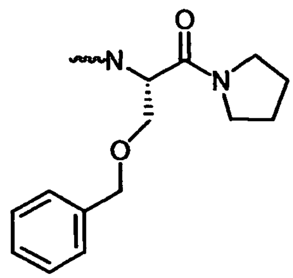
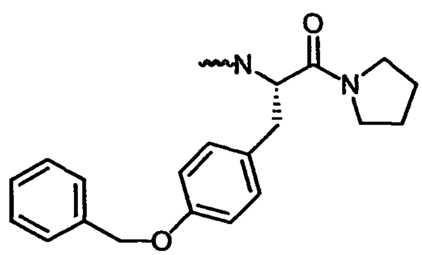
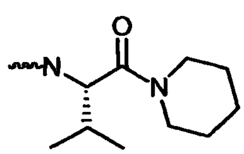
Related Peptide Deformylase Inhibitors

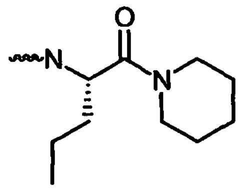
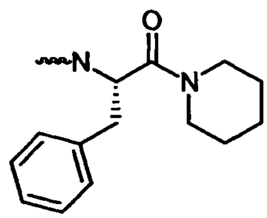
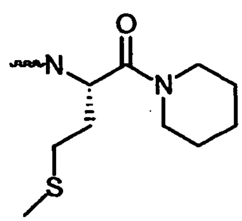
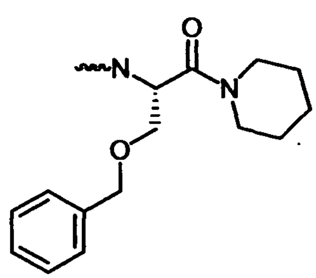


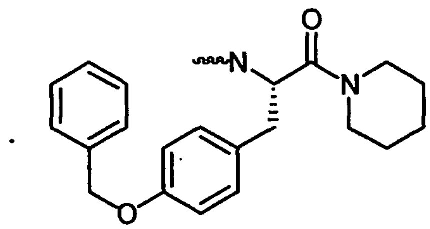
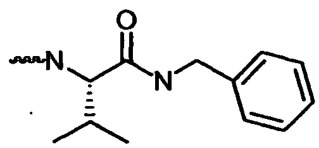
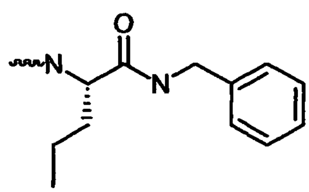
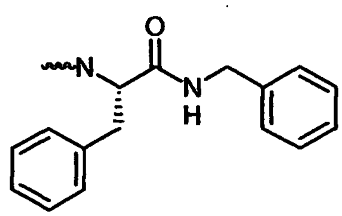
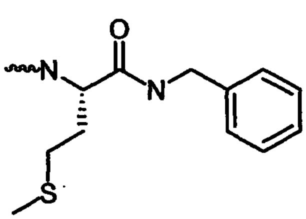
Formula XV

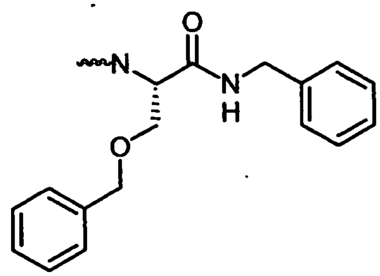
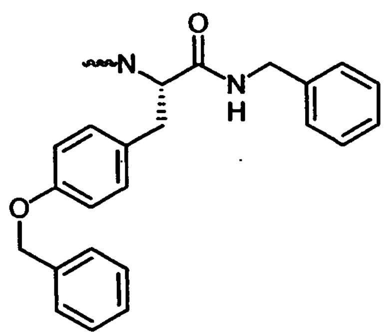
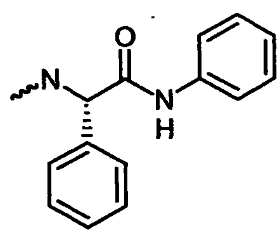
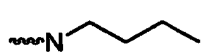
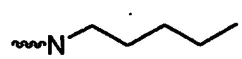
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
137	 Valinyl-pyrrolidinamide	6.1	6.25
138	 Amino-valeryl-N,N-dimethylamide	7.7	——
139	 Phenylalanyl-N,N-dimethylamide	10.1	25

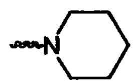
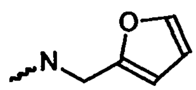
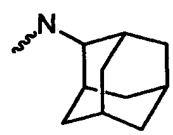
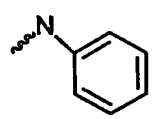
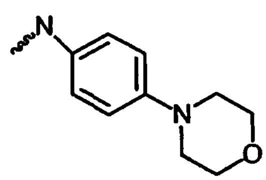
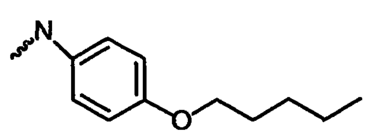
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
140	 Methionyl-N, N-dimethylamide	5.5	——
141	 O-Benzyl-serinyl-N,N-dimethylamide	5.5	50
142	 Benzyl-tyrosinyl-N,N-dimethylamide	10.1	50
143	 Amino-valeryl pyrrolidinamide	5.4	12.5
144	 Phenylalanyl-pyrrolidinamide	11.4	25

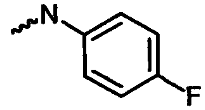
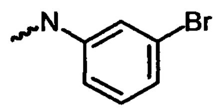
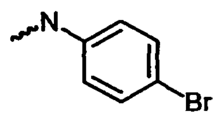
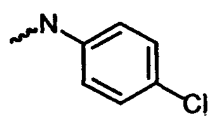
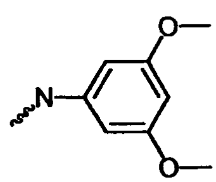
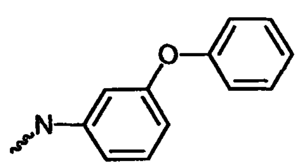
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
145	 Methionyl-pyrrolidinamide	6.0	50
146	 O-Benzyl-serinyl-pyrrolidinamide	6.4	25
147	 O-Benzyl-tyrosinyl-pyrrolidinamide	15	25
148	 Valinyl-piperidinamide	1450	——

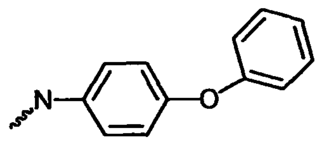
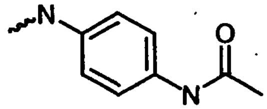
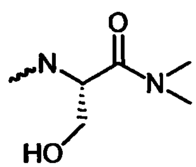
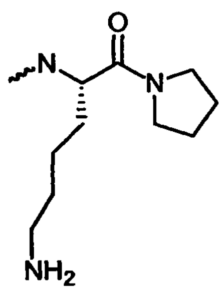
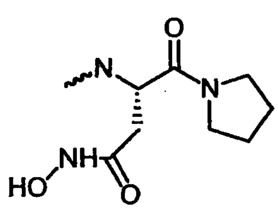
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
149	 Amino-valeryl-piperidinamide	64.0	——
150	 Phenylalanyl-piperidinamide	114.7	100
151	 Methionyl-piperidinamide	222.6	——
152	 O-Benzyl-serinyl-piperidinamide	101.5	25

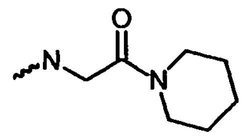
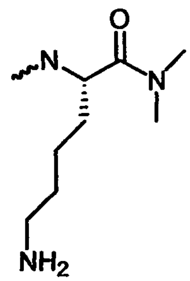
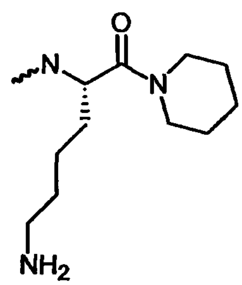
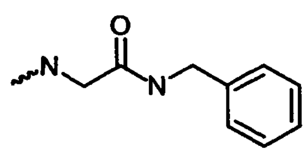
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
153	 O-Benzyl-tyrosinyl-piperidinamide	96.5	——
154	 Valinyl-benzylamide	34.1	25
155	 Amino-Valeryl-benzylamide	7.4	25
156	 Phenylalanyl-benzylamide	6.8	——
157	 Methionyl-benzylamide	26.7	——

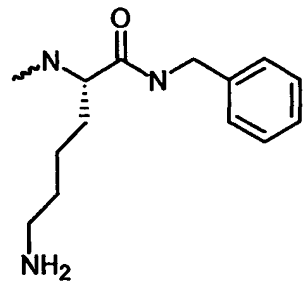
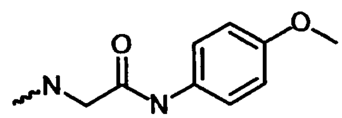
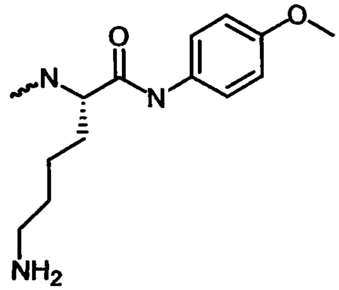
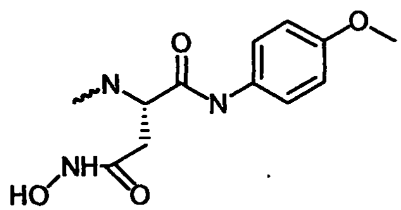
Cmpd No.	R	IC$_{50}$ (nM)	MIC (μg/ml)
158	 O-Benzyl-Tyrosinyl-benzylamide	6.0	——
159	 O-Benzyl-Tyrosinyl-benzylamide	8.6	——
160	 Phenylalanyl-anilinamide	73	100
161	 N-Butylamine	920.5	100
162	 N-Pentylamine	159.8	100

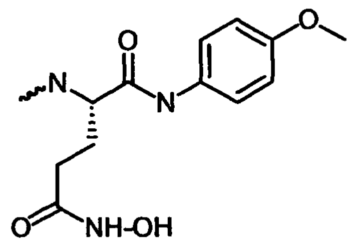
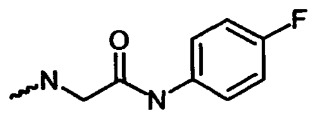
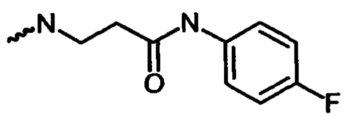
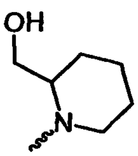
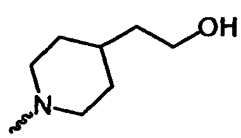
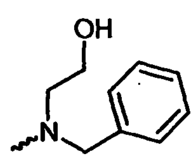
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
163	 N-Pyrrolidine	523.4	100
164	 N-Piperidine	179	100
165	 N-Furfurylamine	120.6	100
166	 N-Adamantylamine	143	100
167	 N-Aniline	408.8	100
168	 N-[4-(Morpholine)]-aniline	1423	100
169	 N-[4-Pentamethyloxy]-aniline	1119	100

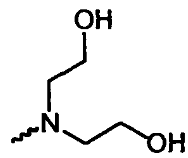
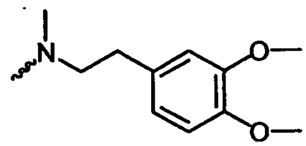
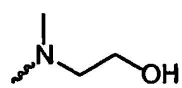
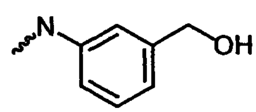
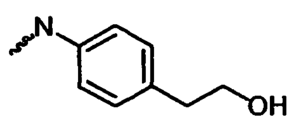
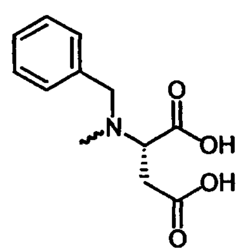
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
170	 N-4-Fluoroaniline	457.7	100
171	 N-3-Bromoaniline	576	100
172	 N-4-Bromoaniline	577	100
173	 N-4-Chloroaniline	542	——
174	 N-3,5-Dimethoxyaniline	547	——
175	 N-3-Phenoxyaniline	1393	——

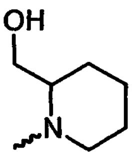
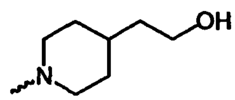
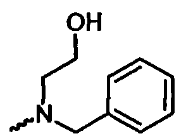
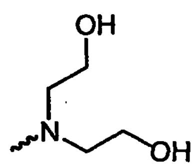
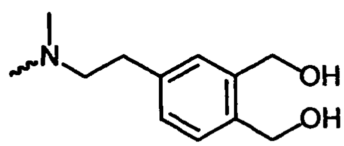
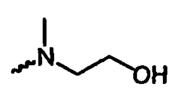
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
176	 N-4-Phenoxyaniline	669	100
177	 N-(4-N-Acetamidyl)-aniline	2553	100
178	 Serinyl-Dimethyl amide	10.9	100
179	 Lysinyl-pyrrolidinamide	7.1	100
180	 Glycinyl-(2-acetohydroxamate)-pyrrolidinamide	13.2	100

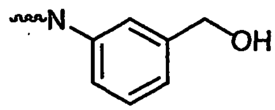
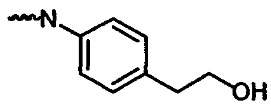
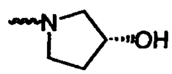
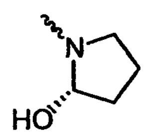
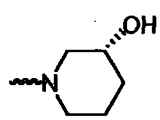
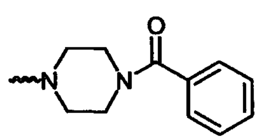
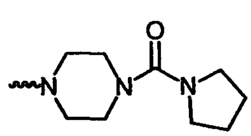
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
181	 Glycinyl-piperidinamide	39.9	100
182	 Lysinyl-dimethyl amide	8.7	100
183	 Lysinyl-piperidinamide	5.1	——
184	 Glycinyl-benzyl amide	146	100

Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
185	 Lysinyl-benzyl amide	35.9	100
186	 Glycinyl-4-methoxy-anilinamide	52	100
187	 Lysinyl-4-methoxy-anilinamide	11	——
188	 Glycinyl (2-acetohydroxyamate) 4-methoxyanilinamide	35	100

Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
189	 Glycinyl-(2-propiohydroxyamate) 4-methoxyanilinamide	8	100
190	 Glycinyl-(4-fluoro)-anilinamide	42	——
191	 N-Propionate (4-fluoro)-anilinamide	172	100
192	 N-2-Piperidine-methanol	30	——
193	 N-4-Piperidine-ethanol	17	——
194	 N-Benzylethanolamine	14	——

Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
195	 N,N-Diethanolamine	200	——
196	 N-Methyl-N-[(3,4-Dimethoxy)-2-phenylethyl]-amine	58	——
197	 N-2-(Methylamino)ethanol	41	——
198	 N-3-Aminobenzyl alcohol	215	——
199	 N-4-Aminophenylethyl alcohol	122	——
200	 N-(N-Benzyl glycinyl-2-ethanoic acid) amine	2030	——

Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
201	 N-2-Piperidine-methanol	30	——
202	 N-4-Piperidine-ethanol	17	——
203	 N-Benzyl-ethanolamine	14	——
204	 N-Diethanolamine	200	——
210	 N-[N-Ethyl-(2-(3,5-dimethoxyphenyl))-N-methyl]amine	58	——
211	 N-2-(Methylamino) ethanol	41	——

Cmpd No.	R	IC$_{50}$ (nM)	MIC (μg/ml)
212	 N-3-Aminobenzyl alcohol	215	——
213	 N-4-Aminophenylethyl alcohol	122	——
214	 3-Pyrrolidinol	89	50
215	 2-Pyrrolidinol	80	25
216	 3-Piperidinol	35	50
217	 N-Piperazine-N-benzylamide	58	100
218	 N-Piperazine-N-pyrrolidinamide	47	50

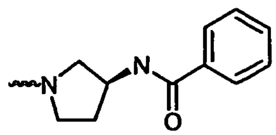
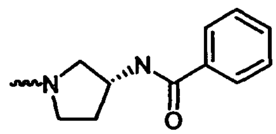
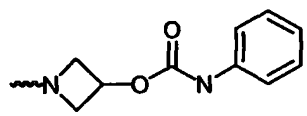
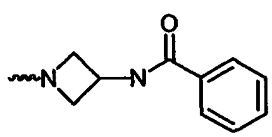
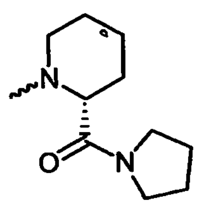
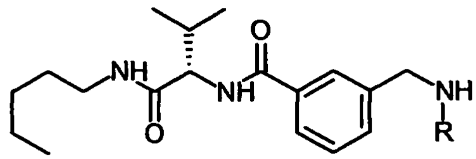
Cmpd No.	R	IC_{50} (nM)	MIC (μg/ml)
219	 N-Pyrrolidine-2(S)-benzylamide	23	100
220	 N-Pyrrolidine-3(R)-benzylamide	39	50
221	 N-Azetidine-(3-O-anilinamide)	33	50
222	 N-3-Benzylamide-azetidine	17	50
223	 N-Piperidine-2-pyrrolidinamide	194	100

Table 12
Capped Valine Series I



Formula XVI

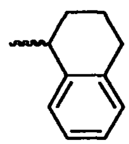
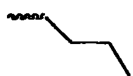
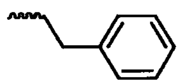
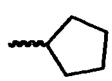
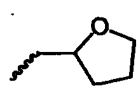
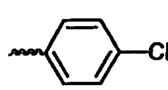
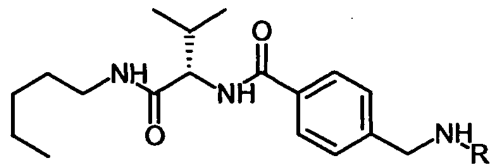
Cmpd No.	R	IC$_{50}$ (nM)
224	 1-Naphthalene-1,2,3,4-tetrahydride	3000
225	 -Butyl	5000
226	 Ethyl 2-phenyl	4500
227	 Cyclopentyl	3500
228	 2-Methyltetrahydrofuran	3500
229	 4-Chlorophenyl	5800

Table 13

Capped Valine Series II



Formula XVII

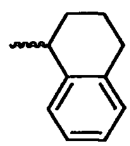
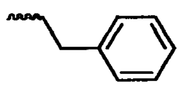
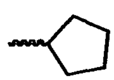
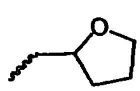
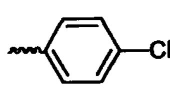
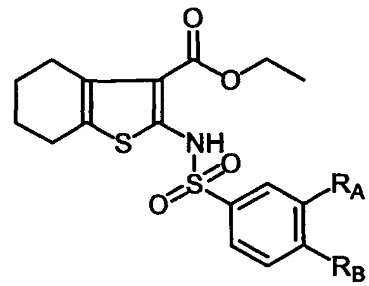
Cmpd No.	R	IC_{50} (nM)
230	 1-Naphthalene-1,2,3,4-tetrahydride	2300
231	 n-Butyl	5200
232	 Ethyl 2-phenyl	4000
233	 Cyclopentyl	1900
234	 2-Methyltetrahydrofuran	1800
235	 4-Chlorophenyl	2000

Table 14

Tetrahydrobenzothiophene Series

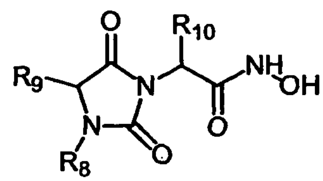


Formula XVIII

Cmpd. No.	R_A	R_B	IC_{50} (nM)
239	$-NO_2$	H	13000
240	H	$-NO_2$	10000
241	H	$-NHC(=O)CH_3$	6000
242	H	-NHC(=O)H	6000
243	H	$-NHS(O_2)CH_3$	9000

Table 15

Hydantoin Series I

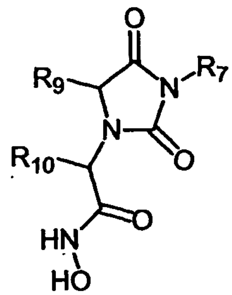


Formula XIX

Cmpd. No.	R_9	R_8	R_{10}	IC_{50}(nM)
244	$-CH_2CH(CH_3)_2$	H	$-(CH_2)_2S(CH_3)$	59,000
245	$-(CH_2)_2S(CH_3)$	H	$-(CH_2)_2S(CH_3)$	127000
246	$-CH(CH_3)_2$	H	$-(CH_2)_2S(CH_3)$	272000
300	$-CH_2(C_6H_5)$	H	$-(CH_2)_2S(CH_3)$	13000
247	$-CH_2(C_6H_5)$	H	$-CH_2(C_6H_5)$	19000
248	$-(CH_2)_3CH_3$	H	$-(CH_2)_2S(CH_3)$	51000
249	$-(CH_2)_3CH_3$	H	$-CH_2C_6H_5$	94000
251	$-CH(CH_3)_2$	H	$-CH(CH_3)_2$	185000
252	$-(CH_2)_2S(CH_3)$	H	$-CH_2CH(CH_3)_2$	74000
253	$-CH_2(C_6H_5)$	H	$-CH_2CH(CH_3)_2$	32000
254	$-(CH_2)_3CH_3$	H	$-CH_2CH(CH_3)_2$	60000

Table 16

Hydantoin Series II



Formula XX

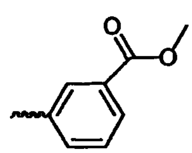
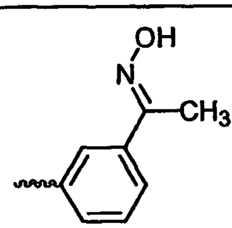
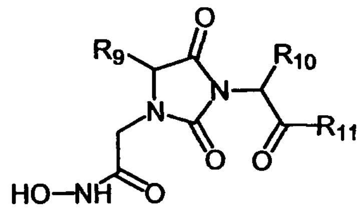
Cmpd. No.	R_7	R_9	R_{10}	IC_{50}(nM)
255	$-CH_3$	$-CH(CH_3)_2$	H	133000
256	$-CH_2(C_6H_5)$	$-(CH_2)_3(CH_3)$	H	3000
257	$-CH_3$	$-(CH_2)_2S(CH_3)$	H	47000
258	$-CH_3$	$-CH_2CH(CH_3)_2$	H	32000
259	$-CH_3$	$-CH_2(C_6H_5)$	H	76000
260	$-CH_3$	$-(CH_2)_3CH_3$	H	24000
250	$-CH_2C(=O)NH-OH$	$-CH(CH_3)_2$	H	75000
261	$-CH_2C_6H_5$	$-CH(CH_3)_2$	H	1000
262	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	H	2000
263	$-CH_2C_6H_5$	$-CH_2C_6H_5$	H	88000
264		$-CH_2CH(CH_3)_2$	H	6520
264A		$-CH_2CH(CH_3)_2$	H	5000

Table 17

Hydantoin Series III

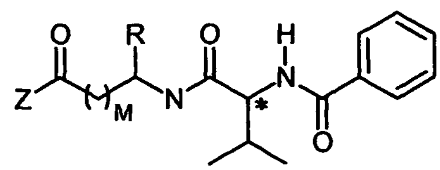


Formula XXII

Cmpd No.	R_9	R_{10}	R_{11}	IC_{50} (nM)
266	$-CH_2CH(CH_3)_2$	H	N-Pyrrolidine	39000
267	$-CH_2CH(CH_3)_2$	H	N-Homopiperidine	10000
301	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	N-Pyrrolidine	1000
268	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	N-Homopiperidine	2000
269	$-(CH_2)_3CH_3$	$-CH(CH_3)_2$	N-Homopiperidine	1000
270	$-CH_2CH(CH_3)_2$	H	N-2-Pyrrolidine-methanol	35000
271	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	N-2-Pyrrolidine-methanol	190
272	$-CH_2CH(CH_3)_2$	$-CH_2(C_6H_5)$	N-2-Pyrrolidine-methanol	400
273	$-CH_2CH(CH_3)_2$	$-CH_2(C_6H_5)$	N-2-Pyrrolidine-methanol	800

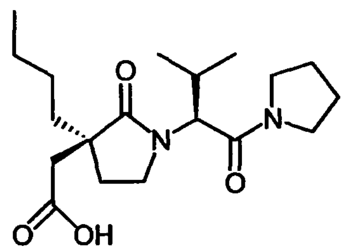
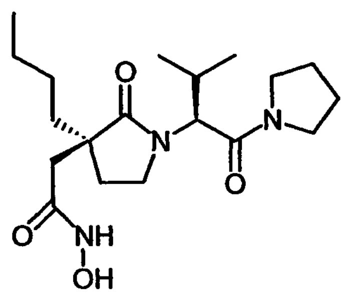
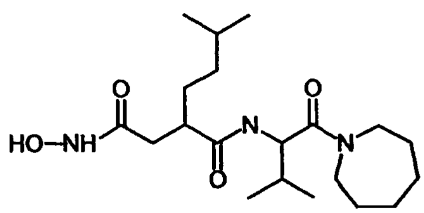
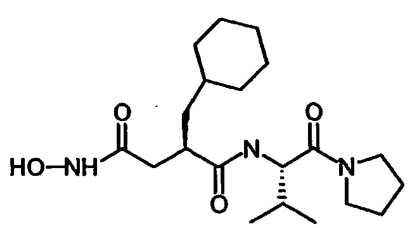
Table 18

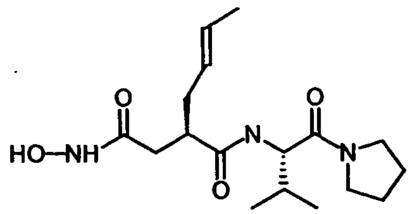
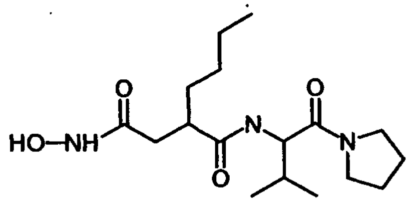
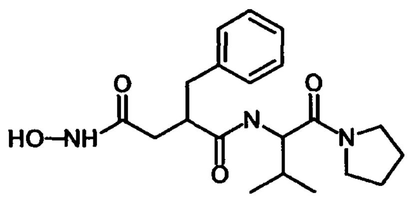
Capped Dipeptide Series III



Cmpd No.	R	0	M	Z	IC_{50} (nM)
274	$-(CH_2)_3CH_3$	L	0	-NH-OH	42
275	$-(CH_2)_3CH_3$	D	0	-NH-OH	502
276	$-CH_2(C_6H_{11})$	L	0	-NH-OH	110
277	$-(CH_2)_3CH_3$	L	1	-NH-OH	100
278	$-(CH_2)_3CH_3$	D	1	-NH-OH	1700
279	$-(CH_2)_3CH_3$	D	1	-OH	1600

Table 19
Related Deformylase Inhibitors

Cmpd No.	Structure	IC_{50} (nM)	MIC (μg/ml)
310		103000	——
311		180	50
312		47	25
313		10	12.5

314		40	12.5
315		30	6.25
316		60	25

4.9 Biological Assays

The compounds of the invention have utility as agents effective against a variety of species of bacteria, including infectious pathogenic bacteria. The invention also includes novel pharmaceutical compositions which comprise the compounds of the invention formulated in pharmaceutically acceptable formulations.

One embodiment the invention features a method for treating a subject infected with an infectious agent by administering to that subject a therapeutically effective amount of a compound of the invention which causes PDF inhibition in the infectious agent as determined by the assays of the invention. Veterinary uses are also included in this embodiment, as described below. Such administration can be by any method known to those skilled in the art, for example, by topical application or by systemic administration. Additional antibacterial compounds may be adjunctively administered, as described below.

In yet another embodiment, compounds of the invention can be used to treat contaminated or infected items, such as crops, wood, metal or plastic and the like, by methods such as, but not limited to, spraying or dusting of that agent onto the contaminated item, or impregnating that agent into the item.

By "therapeutically effective amount" or "prophylactically effective" is meant an amount that relieves (to some extent) one or more symptoms of the disease or condition in the subject. Additionally, by "therapeutically effective amount" is meant an amount that returns to normal, either partially or completely, physiological or biochemical parameters associated with or causative of a bacterial disease or condition.

4.10 Selectivity Profile Assays

High through-put screens described in U.S. application number 09/449,419 filed November 29, 1999, which is incorporated by reference in its entirety, are used to determine the binding affinity of compounds to PDF in a novel assay that utilizes the enzyme's native iron metal center and the binding affinity to several other metalloproteases including thermolysin, carboxypeptidase, collagenase and angiotensin coverting enzyme. The selectivity profile is then determined by calculating the ratio of the binding affinity of the inhibitor to: (1) peptide deformylase with it's native iron metal center and (2) other metalloproteases. It is preferred that compounds bind to PDF with a greater than or equal to 10-fold affinity relative to the other metalloproteases. It is highly preferred that compounds bind to PDF with a greater than or equal to 100-fold affinity relative to the other metalloproteases. In another embodiment, it is preferred that compounds bind to PDF with

a greater than or equal to 100-fold affinity relative to thermolysin and greater than or equal to 300-fold relative to carboxypeptidase, collagenase and angiotensin converting enzyme.

The screening methods of the invention are a substantial improvement over prior technologies in that: (1) the inhibition of peptide deformylase is determined using the enzyme's native iron catalytic metal center and (2) the risk of deleterious side effects can be minimized since the novel inhibitors identified by the means of the invention interact negligibly with important metalloproteases of the host's biochemical machinery. The metalloproteases that are tested include thermolysin, carboxypeptidase, collagenase and angiotensin converting enzyme.

Initial high through-put assays are performed to determine the percent Fe-PDF inhibition at a particular concentration of test compound. The concentration of test compound is typical between 1 μM - 5 mM. While the concentration may be varied, a preferred concentration of test compounds is 300 μM. The concentration of reagents described below reflects assays which contain 300 μM of test compound. However, the concentration of reagents can be easily adjusted to accommodate the concentration of test compound given the parameters provided by the invention in the disclosure below. The reactions are set up in polypropylene plates. Preferred plates have 96- or 384-wells. A preferred plate is a 96-well polypropylene plate with 12 columns and 8 rows. One column is reserved for the negative control (20% DMSO), one column is for the positive control (actinonin, Sigma, St. Louis, MO) and the rest are for test compounds. The reaction mixture, containing CHELEX™ 100 (Sigma, St. Louis, MO) treated water, 10.6 mM NaCl, 1.06 mg/ml BSA, 10.6 mM TCEP-HCl (Pierce, Rockford Il.) 35.3 mM fMAS, 23.5 mM NAD and 17.6 U/ml formate dehydrogenase (FDH) (Roche Molecular Biochemicals, Indianapolis, IN) is agitated and approximately 85 μl of the reaction mixture is then added to each well on the reaction plate. Endpoint data is recorded in a spectrophotometer by monitoring at 335-345 nanometers. 340 nanometers is preferred. To initiate the reactions 10 μl of 1/20,000 fold diluted Fe-PDF (Rajagopalan et al., (1997) *J. Am. Chem. Soc.* 119:12418-12419; Rajagopalan et al., (1997) *Biochemistry* 36:13910-13918, both of which are incorporated by reference) is added to each well. The TCEP buffer is necessary for stabilizing the diluted enzyme. The reaction plate is then mixed on a vortex mixer at low speed. Next the reactions are monitored in a spectrophotometer. A preferred spectrophotometer is the Spectromax 250 (Molecular Devices Corp., Sunnyvale, CA). Analysis of results from these experiments allows the determination of percent inhibition of Fe-PDF at 300 μM test compound.

The assays to determine the binding affinity of the test compounds are based on the results obtained from the percent Fe-PDF inhibition studies. The initial concentrations of the test compounds in the binding affinity assays are adjusted according to the results in the percent Fe-PDF inhibition studies.

Compounds are initially prepared in a 96-well working plate with 12 columns and 8 rows. Again, the invention is not limited to this size plate, one skilled in the art can choose plate size appropriate to ones needs. One column is for the negative control (20% DMSO), another is reserved for the serial dilutions of the positive control, actinonin, and the rest are for the test compounds. The test compounds are diluted from 1/5 to 1/640 fold. 85 μL of reaction mixture is added to each well along with 5 μL of the appropriately diluted test compound. The reactions are initiated by addition of 10 μL of 1/20,000 fold dilute Fe-PDF. After addition of the Fe-PDF the plate is immediately inserted into the spectrophotometer and monitored at 335-345 nanometers and preferably 340 nanometers. Analysis of the data provided from the spectrophotometer readings gives the binding affinities for the test compounds.

The thermolysin assay is designed to detect compounds that have an inhibitory effect on the metalloprotease thermolysin. The assay is based on the use of succinylated casein in conjunction with TNBSA (trinitrobenzene sulfonic acid)(Hatakeyama et al., (1992) *Anal. Biochem.* **204**:181-184; Bubnis et al., (1992) *Anal. Biochem.* **207**:129-133; Habeeb et al., (1996) *Anal. Biochem.* **14**:328-336). Native casein has been treated with succinic anhydride to block available primary amines on the surface of the protein. Thermolysin acts to cleave the peptide bonds to expose primary amines. TNBSA reacts with primary amines to produce a yellow-orange color that can be detected at A430 and quantitated. A control well consisting of substrate, enzyme, and TNBSA with 1% DMSO is used to determine the basal signal level. Any test well with a relative signal lower than the control level would indicate that thermolysin activity has been disrupted. The known inhibitor of thermolysin, phosphoramidon, is added for the calculation IC_{50} data (*i.e.*, the concentration of test compound that results in a fifty percent reduction of enzyme activity).

The carboxypeptidase A assay is designed to detect compounds that have an inhibitory effect on carboxypeptidase A. The assay is based on the use of a blue shift of the absorption spectrum that occurs upon the hydrolysis of a furanacryloyl peptide FAPP (FA-Phe-Phe-OH) by the enzyme (Peterson et al., (1982) *Anal. Biochem.* **125**:420-426, which is incorporated by reference in its entirety). Activity by the enzyme will produce a decrease in OD at A330 between an initial reading at time zero and a second reading after one hour. A control-well consisting of enzyme, substrate, and 1% DMSO is used to

determine a maximum OD. Any test well with an OD lower than the control well will indicate that the enzyme activity has been disrupted. A known inhibitor of Carboxypeptidase A from potato tubers is added for the calculation of IC_{50} data.

The collagenase assay is designed to detect compounds that have an inhibitory effect on bacterial collagenase. The assay is based on the use of a blue shift of the absorption spectrum that occurs upon the hydrolysis of a furanacryloyl peptide FALGPA (FA-Leu-Gly-Pro-Ala-OH) by the enzyme (Van Wart et al., (1981) *Anal. Biochem.* 113:356-365, which is incorporated by reference in its entirety). Activity by the enzyme will produce a decrease in OD at A330 between an initial reading at time zero and a second reading after twenty minutes. A control-well consisting of enzyme, substrate, and 1% DMSO is used to determine a maximum OD. Any test well with a OD lower than the control well would indicate that the enzyme activity has been disrupted. A peptide that is a known inhibitor of collagenase is used for calculation if IC50's.

The angiotensin converting enzyme (ACE) assay is designed to detect compounds that have an inhibitory effect on the enzyme ACE. Angiotensin converting enzyme is a halide-activated peptidase that splits off hydrolytically the dipeptide His-Leu from the carboxyl end of the decapeptide angiotensin I (Asp-Arg-Val-Try-Ile-His-Pro-Phe-His-Leu), thereby converting it to the vasopressor octapeptide angiotensin II. The assay utilizes the internally quenched fluorescent tripeptide derivative Abz-Gly-Phe(NO_2)-Pro. The fluorescent aminobenzoyl (Abz) group incorporated in this tripeptide can be excited in the 300-380 nm range upon cleavage of the peptide bond Gly-Phe(NO_2)-Pro (Carmel and Yaron, (1978) *Anal. Biochem.* 87:265-273, which is incorporated by reference in its entirety). Fluorescence is proportional to the amount of liberated Abz-Gly, and a percent control value can be determined by comparing the fluorescence of a sample compound well to that of a control well containing only 1% DMSO. The substrate has a published $Km = 0.21\ mM \pm\ 0.1\ mM$.

During the course of screens designed to identify inhibitors of peptide deformylase, it was discovered by the present inventors that a variety of compounds inhibit peptide deformylase with a greater than or equal to 10-fold affinity, and preferably a greater than or equal to 100-fold affinity, relative to other metalloproteases.

Determination of MIC

The minimum inhibitory concentration (MIC) against bacterial organisms was determined certain compounds noted herein. Methods known in the art may be used such as broth microdilution testing, using a range of concentrations of each test compound (1993,

National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests For Bacteria That Grow Aerobically - Third Edition: Approved Standard, M7-A3, which is incorporated by reference herein in its entirety). The MIC against a variety of pathogens are determined using the same method. Pathogenic species to be tested generally include, but are not limited to: *E. coli, Enterococcus faecium, Enterococcus faecalis, Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus epidermis, Shigella flexneri*, and *Salmonella typhimurium*.

Formulations

The compounds described above can be provided as pharmaceutically acceptable formulations using formulation methods known to those of ordinary skill in the art. Administration as used in the invention includes those suitable for oral, ophthalmic, (including intravitreal or intracameral), topical, mucosal (including buccal, rectal, vaginal, nasal and sublingual), transdermal or parenteral (including subcutaneous, intramuscular, intravenous, bolus injection, intradermal, intratracheal, by implantabe pump, and epidural) administration. In addition, the combinations may be incorporated into biodegradable polymers allowing for sustained release of the compound, the polymers being implanted in the vicinity of where drug delivery is desired. Biodegradable polymers and their use are described, for example, in detail in Brem et al., *J. Neurosurg.* 74:441-446 (1991).

The formulations include those suitable for oral, rectal, ophthalmic, (including intravitreal or intracameral) nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal, and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into associate the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, etc.

Formulations suitable for topical administration in the mouth include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier.

Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered in a pharmaceutical acceptable carrier.. A preferred topical delivery system is a transdermal patch containing the ingredient to be administered.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of 20 to 500 microns which is administered in the manner in which snuff is administered, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations, wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) conditions requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the administered ingredient.

It should be understood that in addition to the ingredients, particularly mentioned above, the formulations of the present invention may include other agents conventional in

the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents.

Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from about 1 ng to 500 mg of drug per unit dosage. Isotonic saline solutions can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Pharmaceutical compositions thus comprise one or more compounds described above and are associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. Examples of suitable excipients, include but are not limited to lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinlypyrrolidinone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. The compositions can be formulated so as to provide an immediate, sustained or delayed release of active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions of the present invention comprise an antibiotic compound as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients, for example antivirals. The term "pharmaceutically acceptable salts" refers to

salts prepared from pharmaceutically acceptable non-toxic acids and bases, including inorganic and organic acids and bases.

The compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Acids that can be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of the invention are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as, but not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, formate, acetate, propionate, succinate, camphorsulfonate, citrate, acid citrate, fumarate, gluconate, isethionate, lactate, malate, mucate, gentisate, isonicotinate, saccharate, tartrate, bitartrate, para-toluenesulfonate, glycolate, glucuronate, maleate, furoate, glutamate, ascorbate, benzoate, anthranilate, salicylate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, pantothenate, benzenesulfonate, stearate, sulfanilate, alginate, p-toluenesulfonate, and galacturonate. Particularly preferred anions are hydrobromide, hydrochloride, phosphate, acid phosphate, maleate, sulfate, and acid phosphate. Most particularly preferred anions are hydrochloride and maleate.

Compounds of the invention that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds of the invention are those that form non-toxic base addition salts, *i.e.*, salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine, and procaine.

Administration

For administration to subjects, antibiotic compounds of the invention may be formulated in pharmaceutically acceptable compositions. The compositions can be used alone or in combination with one another, or in combination with other therapeutic or diagnostic agents. These compositions can be utilized in vivo, ordinarily in a mammal, preferably in a human, or in vitro. In employing them in vivo, the compositions can be administered to the mammal in a variety of ways, including parenterally, intravenously, subcutaneously, intramuscularly, colonially, rectally, vaginally, nasally, orally, transdermally, topically, ocularly, or intraperitoneally.

As will be readily apparent to one skilled in the art, the magnitude of a therapeutic dose of an antibiotic compound in the acute or chronic management of an infectious disease will vary with the severity of the infection or disease to be treated, the particular composition employed, and the route of administration. The dose and dose frequency will also vary according to the species of animal, age, body weight, condition and response of the individual subject. Such dosing schemes can be readily selected by those skilled in the art with due consideration of such factors.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, an active ingredient can also be administered by controlled release means or delivery devices that are well known to those of ordinary skill in the art, such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, the disclosures of which are incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; and 3) increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and thus can affect the occurrence of side effects.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and gradually and continually

release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various inducers, including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, for example, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PATENT, U.S.A.). An exemplary suitable binder is a mixture of microcrystalline cellulose

and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder/filler in pharmaceutical compositions of the present invention is typically present in about 50 to about 99 weight percent of the pharmaceutical composition.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant will produce tablets which may disintegrate in the bottle. Too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) should be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typically, about 0.5 to about 15 weight percent of disintegrant, preferably about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition.

Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Texas), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass), or mixtures thereof. A lubricant can optionally be added, typically in an amount of less than about 1 weight percent of the pharmaceutical composition.

The methods of the invention also encompass combination therapy in which an antimicrobial compound of the invention or identified by means of the invention is administered as an admixture or sequentially with at least one other antimicrobial. The second antibacterial compound may be naturally occurring or synthetic. Suitable naturally occurring antibacterial compounds include, but are not limited to, aminoglycosides (including but not limited to dihydrostreptomycin, gentamycin, kanamycin, neomycin, paromycin and streptomycin); amphenicols (including but not limited to chloramphenicol); ansamycins (including but not limited to rifamycin); -lactams such as carbapems (including but not limited to imipenem), cephalosporins (including but not limited to cefazedone and cefroxadine), cephamycins (including but not limited to cefbuperazone); monobactams (including but not limited to aztreonam), oxacephems (including but not limited to flomoxef) or penicillins (including but not limited to ampicillin, carbencillin, methicillin, penicillin N, penicillin O and penicillin V); lincosamides (including but not limited to clindamycin and lincomycin); macrolides (including but not limited to carbomycin and erythromycin); polypeptides (including but not limited to gramicidin S); glycopolypeptides (including but not limited to vancomycin and teichoplanin); tetracyclines (including but not limited to apicycline, methacycline and tetracycline); and others such as cycloserine, mupirocin and tuberin. Suitable synthetic antibacterial compounds include 2,4-diaminopyrimidines (including but not limited to trimethoprim); nitrofurans (including but not limited to nifuradene); quinolones and quinolone analogs (including but not limited to enoxacin, lomefloxacin, nalidixic acid and ofloxacin); streptogramins; sulfonamides (including but not limited to sulfamoxole and sulfanilamide); sulfones (including but not limited to diathymosulfone); oxazolidinones (including but not limited to linezolid); and others such as glycylcyclines, clofoctol, hexedine, methenamine, and nitroxoline.

The "adjunct administration" of a compound identified by the method of the invention and a second antibacterial compound means that the two are administered either as a mixture or sequentially. When administered sequentially, the compound may be administered before or after the second antibacterial compound, so long as the initially administered compound is still providing antibacterial activity. Any of the above described modes of administration can be used in combination to deliver the compound and the second antibacterial compound. When a compound identified by the method of the invention and a second antibacterial compound are administered adjunctively as a mixture, they are preferably given in the form of a pharmaceutical composition comprising both agents. Thus, in a further embodiment of the invention, it is provided a pharmaceutical

composition comprising a compound of the invention and a second antibacterial compound together with a pharmaceutically acceptable carrier.

Target Infectious Agents

The antibiotic compounds identified by the methods of the invention can be used to treat infectious diseases in animals, including humans, companion animals (*e.g.*, dogs and cats), livestock animals (*e.g.*, sheep, cattle, goats, pigs, and horses), laboratory animals (*e.g.*, mice, rats, and rabbits), and captive or wild animals.

The antibiotics of the invention selectively target the invading microorganism and thus cause minimal adverse reactions common to many antibiotics such as gastrointestinal disturbances, allergies and hypersensitivities, blood disorders and central nervous system toxicities. The compounds of the invention are expected to be particularly effective against pathogenic organisms found in the blood, muscle tissue (including heart), urinary tract, lower and upper respiratory tract, intestinal, skin and wound, genital tract, and mucosal tissue and include peripheral and central nervous system tissue but are not limited to, gram positive cocci, such as Staphylococci (*e.g.*, S. aureus), Streptococci (*e.g.*, S. pneumoniae, S. pyrogens, S. faecalis, S. viridans); gram positive bacilli, such as Bacillus (*e.g.*, B. anthracis), Corynebacterium (*e.g.*, C. diphtheriae), Listeria (*e.g.*, L. monocytogenes); gram negative cocci, such as Neisseria (*e.g.*, N. gonorrhoeae, N. Meningitidis); gram negative bacilli, such as Haemophilus (*e.g.*, H. influenzae), Pasteurella (*e.g.*, P. multocida), Proteus (*e.g.*, P. mirabilis), Salmonella (*e.g.*, S. typhimurium), Shigella species, Escherichia (*e.g.*, E. coli), Klebsiella (*e.g.*, K. pneumoniae), Serratia (*e.g.*, S. marcescens), Yersinia (*e.g.*, Y. pestis), Providencia species, Enterobacter species, Bacteroides (*e.g.*, fragilis), Acinetobacter species, Campylobacter (*e.g.*, C. jejuni), Pseudomonas (*e.g.*, P. aeruginosa), Bordetella (*e.g.* , B. pertussis), Brucella species, Fracisella (*e.g.*, F. tularensis), Clostridia (*e.g.*, C. perfriugens), Helicobacter (*e.g.*, H. pylori), Vibrio (*e.g.*, V. cholerae), Mycoplasma (*e.g.*, M. pneumoniae), Legionella (*e.g.*, L. pneumophila), Spirochetes (*e.g.*, Treponema, Leptospira and Borrelia), Mycobacteria (*e.g.*, M. tuberculosis), Nocardia (*e.g.*, N. asteroides), Chlamydia (*e.g.*, C. trachomatis), and Rickettsia species.

The following examples serve to further typify the nature of the invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

5. EXAMPLES

The compounds of the invention can be prepared using commercially available starting materials and commercially available reagents using a variety of starting organic transformations. Nevertheless, specific synthetic routes and examples of syntheses are disclosed herein for illustrative purposes.

General

^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz FT-NMR. Preparative HPLC purification was performed on a Gilson HPLC System with 215 autosampler/fraction collector using a Hewlett-Packard 50 x 21.2 mm XDB C18 reverse-phase column running acetonitrile/water gradients at 25 ml/min. Analytical HPLC/MS (electrospray) was performed on a Hewlett-Packard 1100 HPLC with MSD using a MetaChem MetaSil AQ C18 column running acetonitrile/water gradients at 2 mL/min. All anhydrous solvents were purchased from Aldrich chemical company in SureSeal containers. Most reagents were purchase from Aldrich Chemical Company. Protected amino acids were obtained from NovaBiochem.

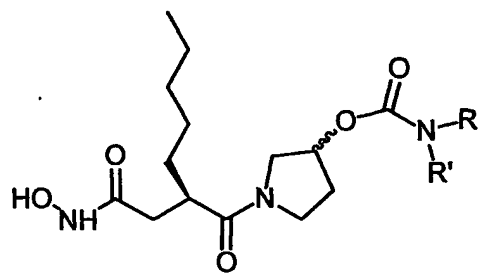
Abbreviations: Boc, tert-butoxycarbonyl; DCE, 1,2-dichloroethane; DCM, dichloromethane; TEA, triethylamine; HOBt, 1-hydroxybenzotriazole; DMAP, dimethylaminopyridine; EDC, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; NHS, N-Hydroxysuccinimide; DMF, dimethylformamide; EtOAc, ethyl acetate; MeOH, methanol; OSu N-hydroxysuccinamide ester; THF, tetrahydrofuran; TFA, trifluoroacetic acid.

Array synthesis was conducted in 15 x 75 mm glass round bottom screw-cap vials contained in a custom 4 x 6 array aluminum synthesis block and sealed with a Teflon-lined rubber membrane. Reagents were added and aqueous extractions performed with single or multichannel pipettors. Filtrations were performed using Whatman/Polyfiltronics 24 well, 10 mL filtration blocks on a Whatman/Polyfiltronics UniVac filtration manifold modified to collect eluent in the custom synthesis block. Evaporation of volatile materials from the array was performed with a Labconco Vortex-Evaporator.

5.1.1 Synthesis of Pyrrolidine Carbamate Series(I)

Compounds represented by Formula VI were synthesized in arrays as described in section 5.1.1. See Scheme I for a general synthetic scheme and Table 1 for representative R groups. The general synthetic scheme involved initial treatment of tert-butyl-(2-pentyl) succinate-mono-N-hydroxysuccinimide ester with 3-pyrrolidinol to afford the

3-hydroxypyrrolidine amide. The tert-butyl group was then removed with subsequent conversion of the carboxylic acid to the methyl ester. The esters were treated with DMAP and various isocyanates were utilized to convert the alcohol to the pyrrolidine carbamates. Finally, the ester moiety was treated with a methanolic solution of hydroxylamine hydrochloride to yield the hydroxamic acid.



Formula VI

Step 1:

To a solution of (R) tert-butyl (2-pentyl)succinate mono N-hydroxysuccinimide ester (1 g, 2.9 mmol) in DCM was added 3-pyrrolidinol (0.51 g, 5.8 mmol). The resulting mixture was stirred at room temperature overnight and evaporated to dryness. The residue was dissolved in EtOAc and washed with 1 N HCl followed by brine. The organic layer was dried over anhydrous sodium sulfate, filtered and solvent removed under reduced pressure. The crude product was purified by column chromatography using EtOAc as eluting solvent. Yield 0.62 g, 68%. ^{1}H NMR (300 MHz, CDCl3) δ: 0.95 (t, 3H), 1.30 (m, 6H), 1.49 (s, 9H), 1.51 (m, 1H), 1.68 (m, 1H), 2.11 (m, 1H), 2.13 (m, 1H), 2.34 (m, 1H), 2.77-3.01 (m, 3H), 3.50-3.80 (m, 3H), 3.95 (m, 1H), 4.56 (m, 1H). HPLC/MS calculated weight 313.44; found 314.4, 335.4 (M+H, M+Na).

Step 2:

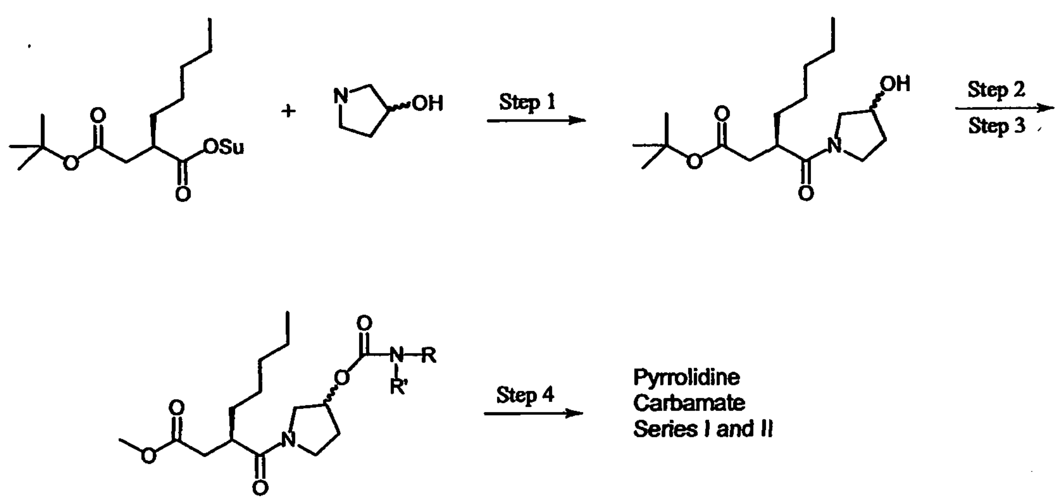
The t-butyl ester (620 mg, 1.98 mmol) was subjected to 10 ml of 20% TFA/DCM solution for 4 h. The solvent was evaporated and dried under high vacuum to yield crude acid. The acid was dissolved in 3 ml of methanol and 6 ml of benzene, and trimethylsilyldiazomethane in hexanes (2.0 M, 6.0 ml, 12 mmol) was added slowly. Volatile material was removed under vacuum and the residue was purified by flash chromatography using 2% MeOH/EtOAc. Yield 480 mg, 90%. ^{1}H NMR (300 MHz, CDCl3) δ: 0.96 (t, 3H), 1.35 (m, 6H), 1.52 (m, 1H), 1.70 (m, 1H), 2.01-2.19 (m, 3H), 2.52 (m, 1H), 2.89-3.04 (m, 2H), 3.55-3.72 (m, 2H), 3.72 (s, 3H), 3.78 (m, 1H), 3.96(m, 1H), 4.58 (m, 1H). HPLC/MS calculated weight 271.36; found 272.4, 294.4 (M+H, M+Na).

Step 3:

To each tube in a 4 x 6 array containing the alcohol ester from the previous reaction (32.5 mg, 0.12 mmol), TEA (33 ml, 0.24 mmol), and DMAP (5 mg) in 2 ml of THF was added an isocyanate (0.36 mmol). The mixtures were agitated and heated at 80°C for 4 h then at 60°C for 12 h, evaporating to dryness. The residue was brought up in 4 ml DCM then washed with 0.5 N aqueous HCl (2 ml) and saturated aqueous NaCl (2 ml). The organic layers were filtered through approximately 0.5 g of anhydrous Na_2SO_4 each and evaporated to dryness. The resulting pyrrolidine carbamates (oils) were each placed in a vacuum chamber under high vacuum overnight, weighed, and analyzed by HPLC/MS.

Step 4:

A methanolic solution of $NH_2OH.HCl$ (2 M, 30 ml) was cooled to 0°C. A methanolic solution of KOH (3 M, 30 ml) was added, the mixture was stirred for 30 min and filtered. An aliquot (2 ml, 2.0 mmol NH_2OH) of this solution was added to each of the reaction vials containing the methyl ester product of the previous reaction. The array was agitated for 30 min. Each solution was acidified to pH = 5-6 with Dowex H^+ resin. The solutions were then filtered and concentrated to dryness. The crude materials were dissolved in 1 ml of DMSO and purified by preparative HPLC. The product-containing fractions were collected, evaporated in a Savant evaporating centrifuge, and re-analyzed by HPLC/MS.



Scheme I

The following compounds were synthesized by the procedure noted in section 5.1.1. The following isocyanates were used: 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl,4-fluoro-phenyl, 2-bromo-phenyl, 3-bromo-phenyl,

phenyl, 4-methoxy-phenyl, 4-trifluoro-methoxy-phenyl, 4-(N,N-Dimethyl-amino)-phenyl, 4-bromo-phenyl, 4-methyl-phenyl, 4-n-butyl-phenyl, 4-trifluoro-methyl-phenyl, 2-methoxy-phenyl, 2-ethyl-phenyl, 2-i-propyl-phenyl, 3-methyl-phenyl, 3-nitro-phenyl, 3-methyl-mercapto-phenyl, 4-chloro-3-nitro-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 2,4-dichloro-phenyl, 2,4-dimethoxy-phenyl, 4-chloro-2-tri-fluoromethyl-phenyl, 2,5-difluoro-phenyl, 2-methoxy-5-chloro-phenyl, 2-methoxy-5-methyl-phenyl, 3,5-dimethyl-phenyl, 3,5-bis-(tri-fluoromethyl)-phenyl, 3,5-dichloro-phenyl, 4-(2,6-dichloro-pyridyl), n-propyl, benzyl, 2-(ethyl-2-thiophene), 4-phenoxy-phenyl, 4-trifluoro-methanemercapto-phenyl, 2-phenyl-phenyl, 2-phenoxy-phenyl.

All compounds were analyzed by HPLC/MS.

Synthesis of compound 1. Calculated weight 425.91, Found 394.2, 427.2, 449.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 2. Calculated weight 425.91, Found 394.2, 427.2, 449.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 3. Calculated weight 425.91, Found 394.2, 427.2, 449.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 4. Calculated weight 409.46, Found 377.4, 410.2, 432.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 5. Calculated weight 409.46, Found 377.4, 410.2, 432.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 6. Calculated weight 409.46, Found 377.4, 410.2, 432.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 7. Calculated weight 470.36, Found 438.0, 471.0, 493.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 8. Calculated weight 470.36, Found 471.0, 493.0 (M+H, M+Na).

Synthesis of compound 9. Calculated weight 391.47, Found 359.2, 392.3, 414.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 10. Calculated weight 421.49, Found 389.2, 422.2, 444.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 11. Calculated weight 475.47, Found 443.2, 476.2, 498.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 12. Calculated weight 434.54, Found 402.4, 435.3, 457.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 13. Calculated weight 470.36, Found 438.0, 471.0, 493.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 14. Calculated weight 405.49, Found 373.3, 406.2, 428.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 15. Calculated weight 447.58, Found 415.3, 448.2, 470.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 16. Calculated weight 459.47, Found 427.1, 482.0 (M-NHOH, M+Na).

Synthesis of compound 17. Calculated weight 421.49, Found 389.2, 422.2, 444.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 18. Calculated weight 419.52, Found 387.2, 420.2, 442.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 19. Calculated weight 433.55, Found 401.2, 434.2, 456.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 20. Calculated weight 405.49, Found 373.3, 406.2, 428.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 21. Calculated weight 436.47, Found 404.0, 437.3, 459.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 22. Calculated weight 437.56, Found 405.2, 438.3, 460.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 23. Calculated weight 470.91, Found 439.2, 472.2, 494.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 24. Calculated weight 493.91, Found 462.0, 495.0, 517.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 25. Calculated weight 460.36, Found 428.0, 461.0, 483.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 26. Calculated weight 451.52, Found 419.2, 452.2, 474.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 27. Calculated weight 493.91, Found 462.0, 495.0, 517.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 28. Calculated weight 427.45, Found 395.2, 428.3, 450.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 29. Calculated weight 455.94, Found 423.1, 457.1, 479.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 30. Calculated weight 435.52, Found 403.3, 436.2, 458.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 31. Calculated weight 419.52, Found 387.2, 420.2, 442.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 32. Calculated weight 527.46, Found 495.0, 528.3, 550.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 33. Calculated weight 460.36, Found 428.0, 461.0, 483.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 34. Calculated weight 461.34, Found 429.0, 462.0, 483.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 35. Calculated weight 357.45, Found 325.4, 358.4, 380.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 36. Calculated weight 405.49, Found 373.4, 406.4, 428.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 37. Calculated weight 425.55, Found 393.2, 426.2, 448.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 38. Calculated weight 483.56, Found 451.2, 484.2, 506.2 (M-NHOH, M+H, M+Na).

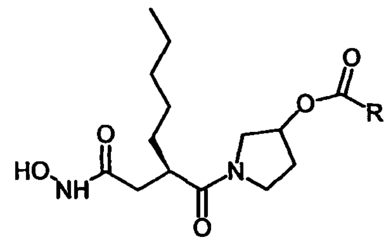
Synthesis of compound 39. Calculated weight 491.53, Found 459.0, 492.0, 514.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 40. Calculated weight 467.57, Found 435.2, 468.2, 490.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 41. Calculated weight 483.56, Found 451.2, 484.2, 506.1 (M-NHOH, M+H, M+Na).

5.1.2 Synthesis of Pyrrolidine Carbamate Series(II)

Compounds represented by Formula VII were synthesized as described in section 5.1.2. See Scheme I for a general synthetic scheme and Table 2 for representative R groups. Synthesis of Series II of the pyrrolidine carbamates was accomplished in an analogous way to Series I, with the exception that in Step 3 secondary amines were used instead of isocyanates.



Formula VII

Step 1:

As in step 1 of the pyrrolidine carbamate I series, section 5.1.1.

Step 2:

As in step 2 of the pyrrolidine carbamate I series, section 5.1.1.

Step 3:

To a solution of triphosgene (78 mg, 0.29 mmol) in anhydrous DCM (2 ml) at 0°C was added the alcohol from Step 2 (78 mg, 0.29 mmol) followed by the addition of TEA (120 ml, 0.87 mmol). The ice bath was removed and resulting mixture was allowed to stir for 4 h. Volatile material was removed in vacuo and residue was taken up in 2 ml of anhydrous DCM. To this solution was added secondary amine (1.44 mmol) and the mixture was allowed to shake for 12 h. The solution was diluted with 2 ml of DCM and washed with 5% aqueous citric acid and brine. The organic layer was dried over sodium sulfate and concentrated to dryness. The crude residue was used in the next step without further purification.

Step 4:

As in step 4 of the pyrrolidine carbamate I series, section 5.1.1.

The following secondary amines were used: N-pyrrolidine, N-pyrrolidine-2-methanol, N-piperidine, N-homo-piperidine, N-morpholine, N-3S-pyrrolidinol

Synthesis of compound 42. Calculated weight 369.46, Found 337.4, 370.4, 392.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 43. Calculated weight 399.49, Found 367.3, 400.4, 422.4 (M-NHOH, M+H, M+Na).

Synthesis of compound 44. Calculated weight 399.49, Found 367.3, 400.3, 422.4 (M-NHOH, M+H, M+Na).

Synthesis of compound 45. Calculated weight 383.49, Found 351.2, 384.2, 406.2 (M-NHOH, M+H, M+Na).

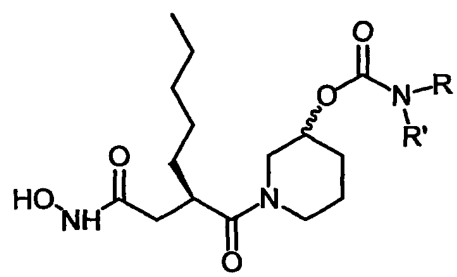
Synthesis of compound 46. Calculated weight 397.52, Found 365.2, 398.3, 420.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 47. Calculated weight 385.46, Found 353.2, 386.2, 408.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 48. Calculated weight 385.46, Found 353.2, 386.2, 408.3 (M-NHOH, M+H, M+Na).

5.2.1 <u>Synthesis of Piperidine Carbamate Series</u>

Compounds represented by Formula X were synthesized as described in section 5.2.1. See Scheme II for general synthetic scheme and Table 3 for representative R groups. The piperidine carbamate series was synthesized analogously to the pyrrolidine series (See 5.1.1 above) replacing 3-pyrrolidinol with 3-hydroxypiperidine hydrochloride salt and proportionate amounts of the other reagents.



Formula X

<u>Step 1:</u>

To a solution of (R) tert-butyl (2-pentyl)succinate mono N-hydroxysuccinimide ester (2 g, 5.86 mmol) in DCM was added 3-hydroxypiperidine hydrochloride (1.6 g, 11.7 mmol) and TEA (2 ml, 14.65 mmol). The resulting mixture was stirred at room temperature overnight and evaporated to dryness. The residue was dissolved with EtOAc

and washed with 1 N HCl followed by brine. The organic layer was dried over anhydrous sodium sulfate, filtered and solvent removed under reduced pressure. The crude product was purified by column chromatography using 75% EtOAc in hexane. Yield 1.75 g, 92%. ^{1}H NMR (300 MHz, CDCl3) δ: 0.95 (t, 3H), 1.34 (m, 6H), 1.50 (s, 9H), 1.57 (m, 4H), 1.86-1.97 (m, 3H), 2.45 (m, 1H), 2.91-2.97 (m, 1H), 3.20-3.23 (m, 1H), 3.49-3.54 (m, 1H), 4.02-4.24 (m, 3H), 4.47 (m, 1H). HPLC/MS calculated weight 327.47; found 328.4, 350.4 (M+H, M+Na).

Step 2:

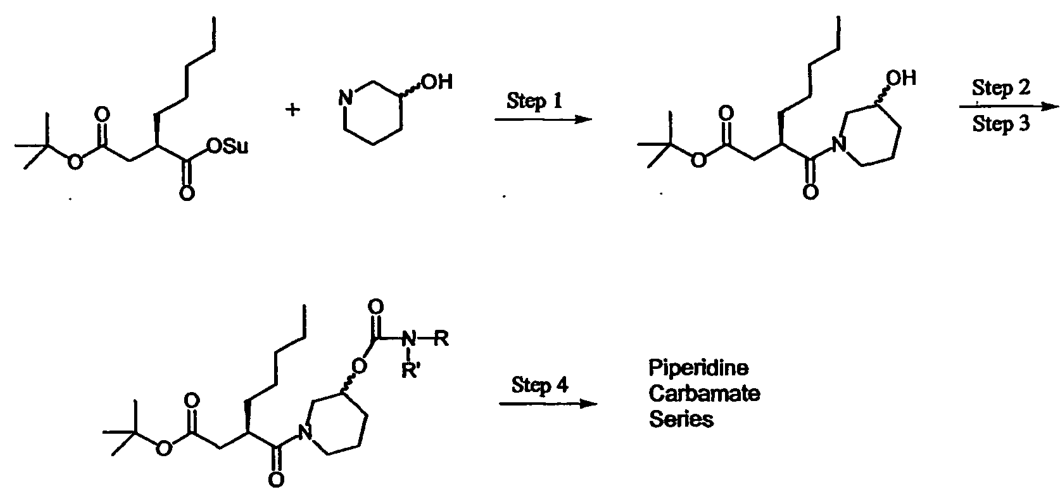
As in Step 2 of pyrrolidine carbamate series, section 5.1.1. Yield 1.05 g , 70%. ^{1}H NMR (300 MHz, CDCl3) δ: 0.95 (t, 3H), 1.34 (m, 6H), 1.51-1.68 (m, 4H), 1.86-1.97 (m, 3H), 2.46 (m,1H), 2.91-3.03 (m, 1H), 3.20-3.26 (m, 1H), 3.49-3.61 (m, 1H), 3.74 (s, 3H), 3.89-4.03 (m, 3H), 4.37 (m,1H). HPLC/MS calculated weight 285.39; found 286.4, 308.4 (M+H, M+Na).

Step 3:

As in step 3 of pyrrolidine carbamate series I, section 5.1.1.

Step 4:

As in step 4 of pyrrolidine carbamate series I, section 5.1.1.



Scheme II

The following isocynanates were used: phenyl, 3,5-di-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 4-methoxy-phenyl, 4-(N,N-di-methylamino)-phenyl, 4-trifluoro-methoxy-phenyl, 4-fluoro-phenyl

Synthesis of compound 49. Calculated weight 405.49, Found 373.3, 406.3, 428.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 50. Calculated weight 474.38, Found 442.2, 475.2, 497.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 51. Calculated weight 439.94, Found 408.1, 441.2, 463.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 52. Calculated weight 439.94, Found 408.1, 441.1, 463.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 53. Calculated weight 435.52, Found 403.3, 436.2, 458.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 54. Calculated weight 448.56, Found 416.2, 449.2, 471.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 55. Calculated weight 489.49, Found 457.2, 490.2, 512.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 56. Calculated weight 423.48, Found 391.2, 424.2, 446.2 (M-NHOH, M+H, M+Na)

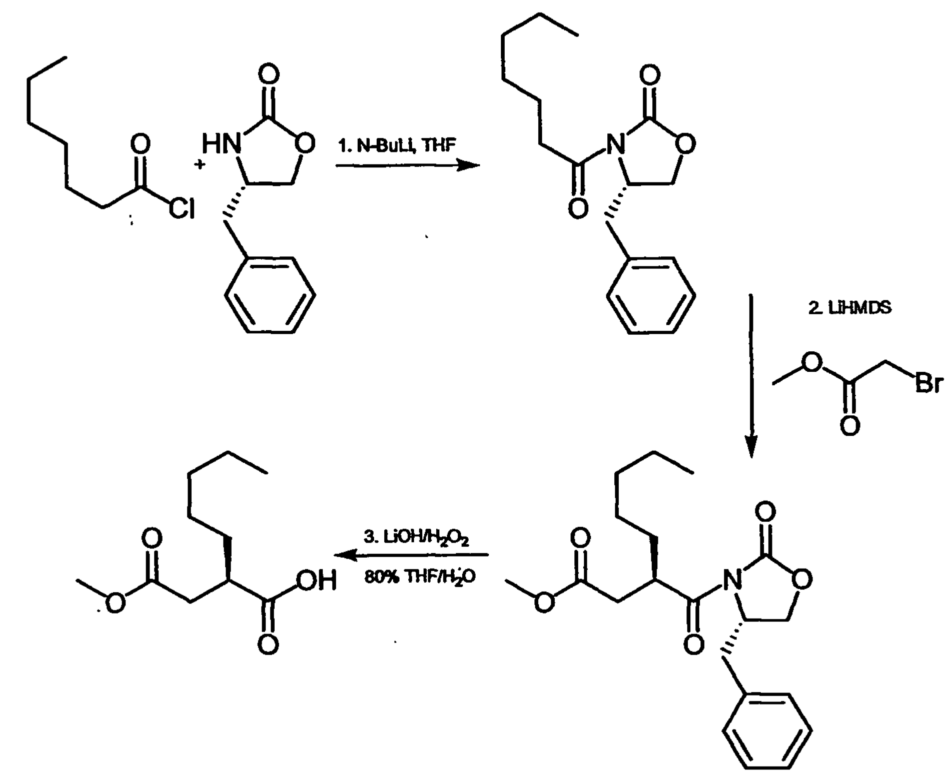
5.2.2 Synthesis of Tic and Pyrrolidine Series

Compounds represented in Table 5 were synthesized as described in section 5.2.2. See Scheme IIIA for general synthetic scheme and Table 5 for representative R groups.

Step 1:

To a solution of (S)-4-Benzyl-2-oxazolidione (6.0 g, 0.034 mol) in dry THF (10 ml/g) at -78°C under argon was added 13.6 ml of n-butyllithium (2.5 M) over 20 min, and the resulting mixture was stirred for 1 h at -78°C. Heptanoyl chloride (5.8 ml, 0.037 mol) was slowly added and allowed to stir at -78°C for 1h and warm to room temperature over an additional 1 h. The reaction was quenched with saturated NH_4Cl (50% total reaction volume), the THF was removed, and the aqueous phase was washed with DCM (2x). The combined organic layers ware washed with 1N NaOH and brine, dried over anhydrous Na_2SO_4. The crude product was obtained after filtration and removal of solvent. The isolated product was utilized in the next step without further purification. Yield: 9.13 g,

93%. Analyzed by ^1H NMR (300MHz, $CDCl_3$): δ 0.82 (t, 3H), 1.27 (m, 6H), 1.59 (m, 2H), 2.69 (dd, 1H), 3.22 (m, 1H), 4.10 (m, 2H), 4.59 (m, 1H), 7.26 (m, 5H). HPLC/MS. Calculated weight 289, Found 290.3, 312.2 (M+H, M+Na).



Scheme IIIA

Step 2:

Lithium hexamethyldisilazide (118 ml, 1M in THF) was cooled to -78°C under argon and a solution of an N-heptanoyloxazolidinone (31g, 0.107 mol) in dry THF (5 ml/g) was added while maintaining the internal reaction temperature below -65°C. After addition, the resulting solution was allowed to stir at -78°C for 1 h. A solution of methyl bromoacetate (24.63g, 0.161 mol) in dry THF (1 ml/g) was added while the internal reaction temperature was maintained below -70°C. The resulting mixture was stirred at -78°C for 3 h and then allowed to warm to -40°C over an additional 1 h. The reaction mixture was then warm to 0°C and quenched with saturated NH_4Cl (50% total reaction volume). The THF was removed under vacuum, and the aqueous phase was washed with EtOAc (2x). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (15% EtOAc/hexane) to give desired product. Yield: 30.07g of pale yellow oil, 78%. Analyzed by : ^1H NMR (300MHz, $CDCl_3$): δ 0.96 (t,

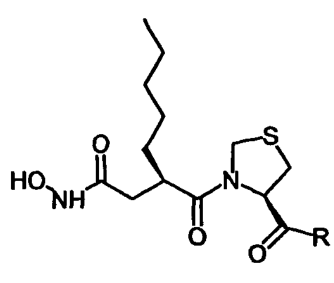
3H), 1.37 (m, 6H), 1.56 (m, 1H), 1.75 (m, 1H), 2.64 (dd, 1H), 2.83 (dd, 1H), 3.00 (dd, 1H), 3.42 (dd, 1H), 3.75 (s, 3H), 4.24 (m, 3H), 4.75 (m, 1H), 7.36 (m, 5H). HPLC/MS. Calculated weight 361, Found 362.3, 384.2 (M+H, M+Na).

Step 3:

An alkylated N-heptanoyloxazolidinones (3.6 g, 0.01 mol) was dissolved in 36 ml of THF/H_2O (4/1, 10 ml/g) and cooled to 0°C. Hydrogen peroxide (30% in water, 6.1 ml, 0.62 ml/mmol) was added followed by a solution of LiOH in water (0.56 g, 0.013 mol, 1.18 M). The reaction mixture was stirred at 0°C for 3 h, after which a solution of Na_2SO_3 in water (1.67 g, 0.013 mol, 2.73 M) was added while maintaining the temperature below 10°C. The THF was removed and the remaining aqueous phase was washed with DCM (2x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2x). The aqueous phase was then acidified to pH = 3 with 1N HCl and washed with EtOAc (3x). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give desired product. Yield 1.5 g, 75%. Analyzed by ^1H NMR (300MHz, $CDCl_3$): δ 0.97 (t, 3H), 1.38 (m, 6H), 1.65 (m, 1H), 1.77 (m, 1H), 2.54 (dd, 1H), 2.80(dd, 1H), 2.96 (m, 1H), 3.78 (s, 3H). HPLC/MS. Calculated weight 202, Found 225.1 (M+Na).

5.2.3 Synthesis of Thioproline Series

Compounds represented by Formula VIII were synthesized as described in section 5.2.2. See Scheme III for a general synthetic scheme and Table 4 for representative R groups. The thioproline series was synthesized with a solution of EDC and HOBT Boc-thioproline and an amine to afford the amino acid amide. To a solution of 2-methylaceto-hexanoic acid with HOBT and EDC was added the amino acid amide. The resulting residue was subsequently treated with hydroxylamine to afford the desired product.



Formula VIII

Synthesis of compound 57.

Step 1 and 2 (Scheme III):

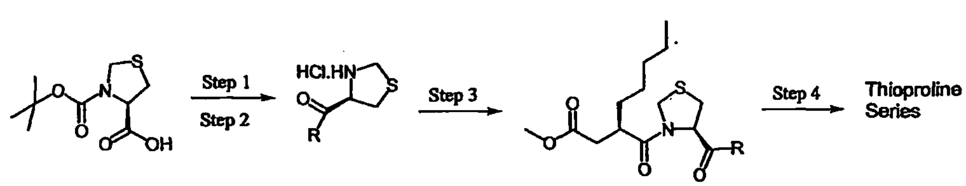
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.290 g, 1.52 mmol) and HOBT (0.256 g, 1.89 mmol) were added to a solution of Boc-thioproline (0.294 g, 1.26 mmol) in DMF (3.75 ml) and agitated for 1 h. Isobutylamine (0.159 ml, 1.6 mmol) was added and the solution was agitated overnight. Saturated ammonium chloride solution was added (5 mL) and the mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, 0.5 N HCl, followed by brine and dried over $NaSO_4$. The solvent was removed in vacuo to give crude Boc aminoamide. The Boc group was removed by treatment with 2 ml of 4.0 M HCl/dioxane for 1 h followed by removal of the solvent in vacuo to give the HCl salt of the amino amide.

Step 3 (Scheme III):

The amino amide HCl salt from Step 1 was added along with triethylamine (0.139 ml, 1.00 mmol) to a solution of (R)-methyl-(2-pentyl)succcinate monoacid (0.050 g, 0.25 mmol), EDC (0.057 g, 0.30 mmol) and HOBT (0.50 g, 0.37 mmol) which had been agitated for 30 min. The resulting mixture was allowed to shake overnight. A saturated solution of ammonium chloride (2.5 ml) was added and the mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, 0.5 N HCl, followed by brine and dried over Na_2SO_4. The solvent was removed in vacuo.

Step 4 (Scheme III):

The residue from Step 3 was dissolved in 2 ml of a solution prepared by mixing equal parts of cold 3 M KOH in methanol and cold 2 M NH_2OH and filtering. This was allowed to shake for 15 min and Dowex H+ resin was added to reach a pH ~ 7. The solution was filtered, concentrated and purified by reverse phase HPLC to give 5.5 mg of Compound 57. Analyzed by HPLC/MS. Calculated weight 373.52, Found 341.1, 374.2, 396.1 (M-NHOH, M+H, M+Na).



Scheme III

Synthesis of compound 58. Synthesis of compound 58 was completed as described above for compound 57 using cyclopentyl amine in place of isobutylamine. Calculated weight 385.53, Found 353.2, 386.2, 408.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 59. Synthesis of compound 59 was completed as described above for compound 57 using cyclohexylamine in place of isobutylamine. Calculated weight 399.55, Found 367.3, 400.2 (M-NHOH, M+H).

Synthesis of compound 60. Synthesis of compound 60 was completed as described above for compound 57 using terahydrofurfuryl-amine in place of isobutylamine. Calculated weight 401.53, Found 369.2, 402.2, 424.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 61. Synthesis of compound 61 was completed as described above for compound 57 using furfurylamine in place of isobutylamine. Calculated weight 39.50, Found 365.1, 398.1, 420.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 62. Synthesis of compound 62 was completed as described above for compound 57 using 2-thiophenmethylamine in place of isobutylamine. Calculated weight 413.56, Found 381.0, 414.1, 436.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 63. Synthesis of compound 63 was completed as described above for compound 57 using benzylamine in place of isobutylamine. Calculated weight 407.53, Found 375.2, 408.3, 430.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 62. Synthesis of compound 64 was completed as described above for compound 57 using 2-aminothiazole in place of isobutylamine. Calculated weight 400.52, Found 368.0, 401.0, 423.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 65. Synthesis of compound 65 was completed as described above for compound 57 using dimethylamine in place of isobutylamine. Calculated weight 345.46, Found 313.2, 346.3, 368.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 66. Synthesis of compound 66 was completed as described above for compound 57 using pyrrolidine in place of isobutylamine. Calculated weight 371.50, Found 339.2, 372.2, 394.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 67. Synthesis of compound 67 was completed as described above for compound 57 using piperidine in place of isobutylamine. Calculated weight 385.53, Found 353.2, 386.2, 408.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 68. Synthesis of compound 68 was completed as described above for compound 57 using hexamethylineimine in place of isobutylamine. Calculated weight 399.55, Found 367.3, 400.2, 422.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 69. Synthesis of compound 69 was completed as described above for compound 57 using morpholine in place of isobutylamine. Calculated weight 387.50, Found 355.2, 388.2, 410.1 (M-NHOH, M+H, M+Na).

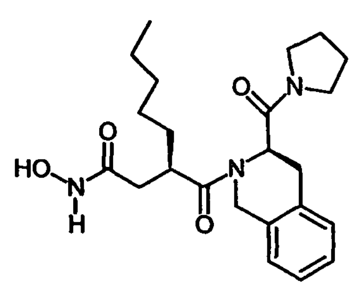
Synthesis of compound 70. Synthesis of compound 70 was completed as described above for compound 57 using 2,6-dimethylmorpholine in place of isobutylamine. Calculated weight 415.55, Found 383.2, 416.2, 438.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 71. Synthesis of compound 71 was completed as described above for compound 57 using thiomorpholine in place of isobutylamine. Calculated weight 403.57, Found 371.0, 404.2, 426.0 (M-NHOH, M+H, M+Na).

5.2.3 Synthesis of Tic and Proline Series

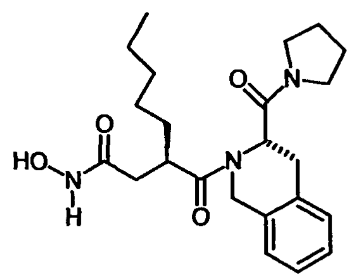
Compounds of the formulas listed below were synthesized in a manner similar to the thioproline series. See section 5.2.2 and Table 5 for representative R groups.

Synthesis of compound 72. Synthesis of compound 72 was completed as described above for compound 57 using Boc-D-tetrahydroisoquinoline in place of Boc-thioproline. Calculated weight 415.54, Found 345.2, 416.2 (M-pyrrolidine, M+H).



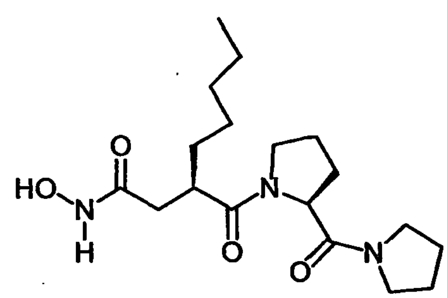
Compound 72

Synthesis of compound 73. Synthesis of compound 73 was completed as described above for compound 57 using Boc-tetrahydroisoquinoline in place of Boc-thioproline. Calculated weight 415.54, Found 345.1, 438.3 (M-pyrrolidine, M+Na).



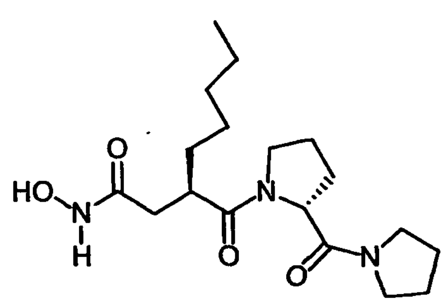
Compound 73

Synthesis of compound 74. Synthesis of compound 74 was completed as described above for compound 57 using Boc-L-proline in place of Boc-thioproline. Calculated weight 353.47, Found 321.2, 354.2 (M-NHOH, M+H).



Compound 74

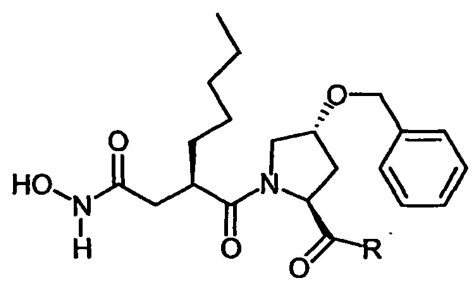
Synthesis of compound 75. Synthesis of compound 75 was completed as described above for compound 57 using Boc-D-proline in place of Boc-thioproline. Calculated weight 353.47, Found 321.2, 354.2 (M-NHOH, M+H).



Compound 75

5.2.4 Synthesis of Benzyloxyproline Series

Compounds of the benzyloxproline series, Formula IX were synthesized in a manner similar to the thioproline series. See section 5.2.3 and Table 6 for representative R groups.



Formula IX

Synthesis of compound 76. Synthesis of compound 76 was completed as described above for compound 64 using Boc-3-benzyloxyproline in place of Boc-thioproline. Calculated weight 488.61, Found 456.1; 489.2 (M-NHOH, M+H).

Synthesis of compound 77. Synthesis of compound 77 was completed as described above for compound 65 using Boc-3-benzyloxyproline in place of Boc-thioproline. Calculated weight 433.55, Found 401.2, 434.2 (M-NHOH, M+H).

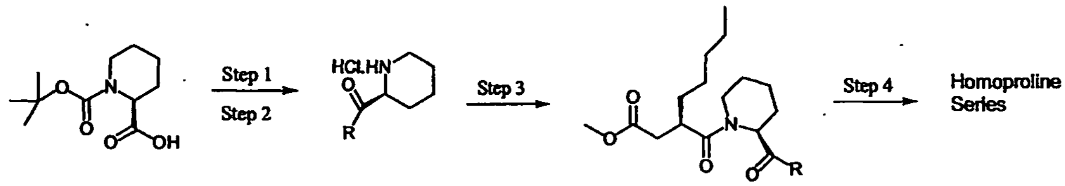
Synthesis of compound 78. Synthesis of compound 78 was completed as described above for compound 87 using Boc-3-benzyloxyproline in place of Boc-homoproline. Calculated weight 495.62, Found 463.3, 496.3 (M-NHOH, M+H).

Synthesis of compound 79. Synthesis of compound 79 was completed as described above for compound 58 using Boc-3-benzyloxyproline in place of Boc-thioproline. Calculated weight 473.62, Found 441.2, 474.2 (M-NHOH, M+H).

Synthesis of compound 80. Synthesis of compound 80 was completed as described above for compound 71 using Boc-3-benzyloxyproline in place of Boc-thioproline. Calculated weight 491.65, Found 469.3, 492.3 (M-NHOH, M+H).

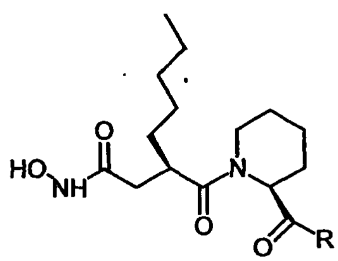
5.2.5 Synthesis of Homoproline Series I

Compounds represented by Formula X are synthesized as described in section 5.2.2. See Scheme IV for a general synthetic scheme and Table 7 for representative R groups. The



Scheme IV

homoproline series was synthesized in an analogous fashion to the thioproline series, with Boc-thioproline replaced by Boc-pipecolic acid.



Formula X

Synthesis of compound 81. Synthesis of compound 81 was completed as described above for compound 57 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 369.50, Found 337.2, 392.3 (M-NHOH, M+Na).

Synthesis of compound 82. Synthesis of compound 82 was completed as described above for compound 58 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 381.52, Found 349.2, 404.3 (M-NHOH, M+Na).

Synthesis of compound 83. Synthesis of compound 83 was completed as described above for compound 59 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 395.54, Found 363.3, 418.2 (M-NHOH, M+Na).

Synthesis of compound 84. Synthesis of compound 84 was completed as described above for compound 60 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 397.52, Found 365.2, 420.0 (M-NHOH, M+Na).

Synthesis of compound 85. Synthesis of compound 85 was completed as described above for compound 61 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 393.48, Found 361.2, 416.2 (M-NHOH, M+Na).

Synthesis of compound 86. Synthesis of compound 86 was completed as described above for compound 62 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 409.55, Found 377.2, 432.2 (M-NHOH, M+Na).

Synthesis of compound 87. Synthesis of compound 87 was completed as described above for compound 57 using Boc-pipecolic acid in place of Boc-thioproline and 2-aminomethylpyridine in place of isobutylamine. Calculated weight 404.51, Found 405.2, 427.2 (M+H, M+Na).

Synthesis of compound 88. Synthesis of compound 88 was completed as described above for compound 63 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 403.52, Found 371.1, 426.2(M-NHOH, M+Na).

Synthesis of compound 89. Synthesis of compound 89 was completed as described above for compound 64 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 396.51, Found 397.2, 419.0 (M+H, M+Na).

Synthesis of compound 90. Synthesis of compound 90 was completed as described above for compound 65 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 341.45, Found 364.2, (M+Na).

Synthesis of compound 91. Synthesis of compound 91 was completed as described above for compound 67 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 381.52, Found 349.2, 404.2 (M-NHOH, M+Na).

Synthesis of compound 92. Synthesis of compound 92 was completed as described above for compound 68 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 395.54, Found 363.2, 418.2 (M-NHOH, M+Na).

Synthesis of compound 93. Synthesis of compound 93 was completed as described above for compound 69 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 383.49, Found 406.2, (M+Na).

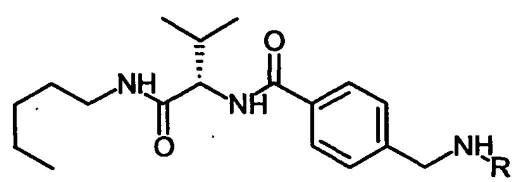
Synthesis of compound 94. Synthesis of compound 94 was completed as described above for compound 70 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 411.54, Found 434.2, (M+Na).

Synthesis of compound 95. Synthesis of compound 95 was completed as described above for compound 71 using Boc-pipecolic acid in place of Boc-thioproline. Calculated weight 399.55, Found 367.3, 422.2, (M-NHOH, M+Na).

Synthesis of compound 96. Synthesis of compound 96 was completed as described above for compound 57 using Boc-pipecolic acid in place of Boc-thioproline and N-methyl piperazine in place of isobutylamine. Calculated weight 396.53, Found 397.2, 420.2 (M+H, M+Na).

5.5.1 Synthesis of Compounds of Formula XVII

Compounds represented by Formula XVII are synthesized as described in section 5.5.1. See Table 13 for representative R groups.



Formula XVII

Synthesis of compound 97. Synthesis of compound 97 was completed as described above for compound using Boc-pipecolic acid in the place of Boc-thioproline and pyrrolidine.

Step 1:

EDC (4 g, 20.86 mmol) and HOBT (4 g, 29.6 mmol) were added to a solution of Boc-pipecolic acid (4 g, 17.44 mmol) in DMF (60 ml) and stirred for 1 h. Isobutylamine (0.159 ml, 1.6 mmol) was added and the solution was stirred overnight. Saturated ammonium chloride solution was added (200 ml) and the mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, 0.5 NH_2Cl, brine and dried

over Na_2SO_4. The solvent was removed in vacuo to give desired product. The Boc group was removed by treatment with 16 ml of 4.0 M HCl/dioxane for 2 h followed by removal of the solvent in vacuo to give the HCl salt of the amino amide. Crude Yield 3.4 g, quantitative.

Step 2:

This amino amide HCl salt (1.48 g, 6.76 mmol) was added along with triethylamine (0.139 ml, 1.00 mmol) to a solution of (R) tert-butyl (2-pentyl)succinate mono acid (1.5 g, 6.15 mmol), EDC (1.41 g, 7.38 mmol) and HOBT (1.40 g, 10.36 mmol) which had been stirred in 50 ml of DMF for 30 min. The resulting mixture was allowed to stir overnight. A saturated solution of ammonium chloride (2.5 ml) was added and the mixture was extracted with EtOAc. The organic layer washed with saturated $NaHCO_3$, 0.5 NHCl, brine and dried over Na_2SO_4. The solvent was removed in vacuo to give crude oil which was purified by flash chromatography using 50% EtOAc in hexane. Yield 2.15g, 86%. Analyzed by LC/MS Calculated weight 408.59; Found 338.3, 431.3 (M-C4H8N, M+Na).

Step 3:

The tert-butyl ester (1.6 g, 3.92 mmol) was subjected to 15 ml of 20% TFA in DCM and stirred for 1 h. Evaporation and dried under high vacuum to yield crude acid which was dissolved in 6 ml of methanol and 12 ml of benzene, and trimethylsilyldiazomethane in hexanes (2.0 M, 12.0 ml, 24 mmol) was added slowly. Volatile material was removed in vacuo and the residue was purified by flash chromatography using EtOAc. Yield 1.05 g, 70%. Analyzed by LC/MS. Calculated weight 366.50; Found 296.3, 389.2 (M-C4H8N, M+Na).

Step 4:

A methanolic solution of NH_2OH HCl (2 M, 30 ml) was cooled to 0°C. A methanolic solution of KOH (3 M, 30 ml) was added dropwise over 30 min, the mixture was stirred for 30 min and filtered. An aliquot (10 ml, 20 mmol NH_2OH) of this solution was added to the methyl ester (0.35 g, 0.95 mmol); product of the previous reaction. The mixture was allowed to shake for 30 min and acidified to pH 5 by Dowex acidic resin. The solvent was removed in vacuo and the residue was purified by flash chromatography using 5% MeOH in EtOAc. Yield 175 mg, 50%. Analyzed by LC/MS. Calculated weight 367.49; Found 297.2, 390.2 (M-C4H8N, M+Na).

Synthesis of compound 223 was completed as described above for compound 97 using D-Boc-pipecolic acid in place of L-Boc-pipecolic. Analyzed by HPLC/MS. Calculated weight 367.49, Found 297.2, 368.3 (M-C4H8N, M+H).

Synthesis of compound 98. Synthesis of compound 98 was completed as described above for compound 97 using (R)-2-(t-butylcarboxymethyl)-3-(3,4-difluorophenyl)-propionic acid in place of (R) tert-butyl (2-pentyl) succinate mono acid. Analyzed by HPLC/MS. Calculated weight 423.46, Found 446.1 (M+Na).

Synthesis of compound 99. Synthesis of compound 99 was completed as described above for compound 97 using (R)-2-(t-butylcarboxymethyl)-3-phenylmethylpropionic acid in place of (R) tert-butyl (2-pentyl) succinate mono acid. Analyzed by HPLC/MS. Calculated weight 387.48, Found 410.2 (M+Na).

Synthesis of compound 100. Synthesis of compound 100 was completed as described above for compound 97 using (R)-2-(t-butylcarboxymethyl)-3-cyclohexylmethylpropionic acid in place of (R) tert-butyl (2-pentyl) succinate mono acid. Analyzed by HPLC/MS. Calculated weight 393.53, Found 416.2 (M+Na).

Synthesis of compound 101. Synthesis of compound 101 was completed as described above for compound 97 using (R)-2-(t-butylcarboxymethyl)-3-(3,4-difluorophenyl)-propionic acid in place of (R) tert-butyl (2-pentyl) succinate mono acid and 2-aminothiazole in place of pyrrolidine. Analyzed by HPLC/MS. Calculated weight 452.48, Found 453.0, 475.0 (M+H, M+Na).

Synthesis of compound 102. Synthesis of compound 102 was completed as described above for compound 97 using (R)-2-(t-butylcarboxymethyl)-3-phenylmethylpropionic acid in place of (R) tert-butyl (2-pentyl) succinate mono acid and 2-aminothiazole in place of pyrrolidine. Analyzed by HPLC/MS. Calculated weight 416.50, Found 417.1, 439.0 (M+H, M+Na).

Synthesis of compound 103. Synthesis of compound 103 was completed as described above for compound 97 using (R)-2-(t-butylcarboxymethyl)-3-cyclohexylmethylpropionic acid in place of (R) tert-butyl (2-pentyl) succinate mono acid and 2-aminothiazole in place of pyrrolidine. Analyzed by HPLC/MS. Calculated weight 422.55, Found 423.1, 445.1(M+H, M+Na).

Synthesis of compound 120A

Step 1:

To a solution of (R) tert-butyl (2-pentyl)succinate mono N-hydroxysuccinimide ester (0.34 g, 1 mmol) in DCM was added N,N Diethylnipecotic acid (372 ml, 2.0 mmol) and TEA (2 ml, 14.65 mmol). The resulting mixture was stirred at room temperature for overnight and evaporated to dryness. The residue was taken up with EtOAc and extracted with 1 N HCl then brine. The organic layer was dried over anhydrous sodium sulfate, filtered and solvent removed under reduced pressure to give 0.48 g of crude product which was carried to next step without further purification.

Step 2:

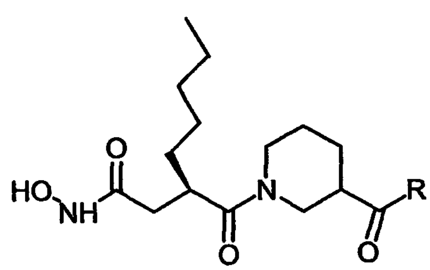
Same as step 3 in the synthesis of compound 97

Step 3:

Same as step 4 in the synthesis of compound 97

5.2.6 Synthesis of Nipecotic Acid Series

Compounds represented by Formula XII were synthesized as described in section 5.2.2. See Scheme V for a general synthetic scheme and Table 9 for representative R groups. The nipecotic acid series was synthesized in an analogous fashion to the thioproline series (See 5.2.2 above), with Boc-thioproline replaced by Boc-nipecotic acid.



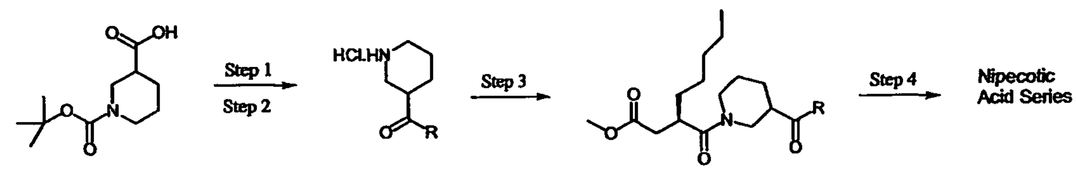
Formula XII

Synthesis of compound 104. Synthesis of compound 104 was completed as described above for compound 57 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 369.50, Found 337.2, 370.2, 392.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 105. Synthesis of compound 105 was completed as described above for compound 58 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 381.52, Found 349.2, 382.3, 404.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 106. Synthesis of compound 106 as completed as described above for compound 59 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 395.54, Found 363.3, 396.3, 418.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 107. Synthesis of compound 107 was completed as described above for compound 60 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 397.52, Found 365.2, 398.3, 420.2 (M-NHOH, M+H, M+Na).



Scheme V

Synthesis of compound 108. Synthesis of compound 108 was completed as described above for compound 61 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 393.48, Found 361.2, 394.2, 416.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 109. Synthesis of compound 109 was completed as described above for compound 62 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 409.55, Found 377.2, 410.2, 432.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 110. Synthesis of compound 110 was completed as described above for compound 57 using Boc-nipecotic acid in place of Boc-thioproline and 2-aminomethylpyridine in place of isobutylamine. Calculated weight 404.51, Found 372.3, 405.2, 427.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 111. Synthesis of compound 111 was completed as described above for compound 63 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 403.52, Found 371.2, 404.2, 426.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 112. Synthesis of compound 112 was completed as described above for compound 64 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 396.51, Found 364.1, 397.2, 419.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 113. Synthesis of compound 113 was completed as described above for compound 65 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 341.45, Found 309.2, 342.2, 364.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 114. Synthesis of compound 114 was completed as described above for compound 66 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 367.49, Found 335.2, 368.3, 390.0 (M-NHOH, M+H, M+Na).

Synthesis of compound 115. Synthesis of compound 115 was completed as described above for compound 67 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 381.52, Found 349.2, 382.3, 404.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 116. Synthesis of compound 116 was completed as described above for compound 69 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 395.54, Found 363.3, 396.3, 418.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 117. Synthesis of compound 117 was completed as described above for compound 70 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 383.49, Found 351.2, 384.2, 406.2 (M-NHOH, M+H, M+Na).

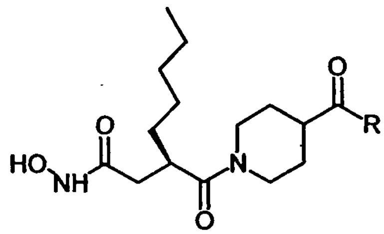
Synthesis of compound 118. Synthesis of compound 118 was completed as described above for compound 70 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 411.54, Found 379.2, 412.3, 434.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 119. Synthesis of compound 119 was completed as described above for compound 71 using Boc-nipecotic acid in place of Boc-thioproline. Calculated weight 399.55, Found 367.3, 400.2, 422.1 (M-NHOH, M+H, M+Na).

Synthesis of compound 120. Synthesis of compound 120 was completed as described above for compound 57 using Boc-nipecotic acid in place of Boc-thioproline and N-methyl piperazine in place of isobutylamine. Calculated weight 396.53, Found 364.2, 397.2 (M-NHOH, M+H).

5.2.7 Synthesis of Isonipecotic Acid Series

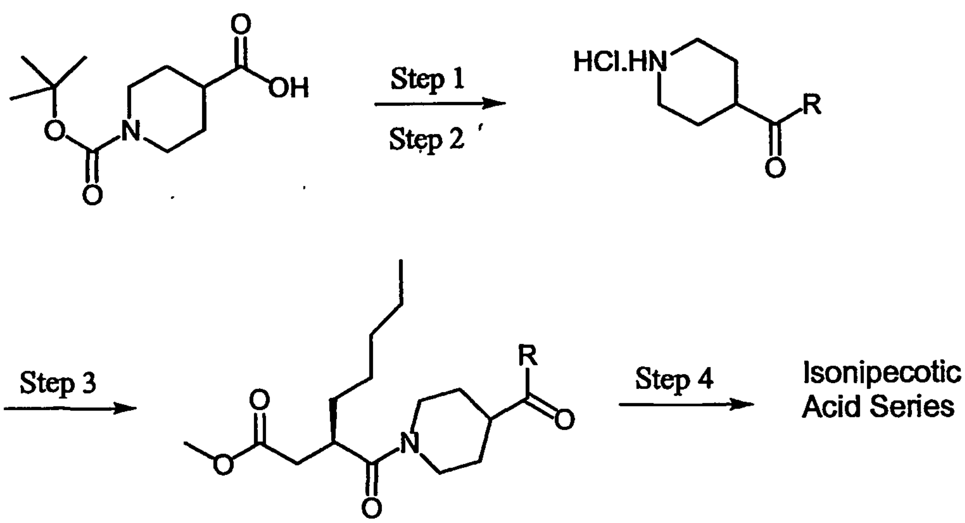
Compounds represented by Formula XIII are synthesized as described in section 5.2.2. See Scheme VI for a general synthetic scheme and Table 10 for representative R groups. The isonipecotic acid series was synthesized in an analogous fashion to the thioproline series, wherein Boc-thioproline replaced with Boc-isonipacotic acid.



Formula XIII

Synthesis of compound 123. Synthesis of compound 123 was completed as described for compound 59 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 369.51, Found 337.2, 370.2, 392.3 (M-NHOH, M+H, M+Na).

Synthesis of compound 124. Synthesis of compound 124 was completed as described for compound 58 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 381.52, Found 349.2, 382.3 (M-NHOH, M+H).



Scheme VI

Synthesis of compound 125. Synthesis of compound 125 was completed as described for compound 61 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 393.49, Found 361.2, 394.2 (M-NHOH, M+H).

Synthesis of compound 126. Synthesis of compound 126 was completed as described for compound 62 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 409.55, Found 377.2, 410.2 (M-NHOH, M+H).

Synthesis of compound 127. Synthesis of compound 127 was completed as described for compound 57 above for using Boc-isonipecotic acid in place of Boc-thioproline and 2-aminomethylpyridine in place of isobutylamine. Calculated weight 404.51, Found 372.3, 405.2 (M-NHOH, M+H).

Synthesis of compound 128. Synthesis of compound 128 was completed as described for compound 63 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 403.53, Found 371.2, 404.2, 426.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 129. Synthesis of compound 129 was completed as described for compound 64 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 369.51, Found 364.2, 397.2 (M-NHOH, M+H).

Synthesis of compound 130. Synthesis of compound 130 was completed as described for compound 65 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 341.45, Found 309.2, 342.3, 364.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 131. Synthesis of compound 131 was completed as described for compound 66 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 367.49, Found 335.2, 368.3, 390.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 132. Synthesis of compound 132 was completed as described for compound 67 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 381.52, Found 349.2, 382.3 (M-NHOH, M+H).

Synthesis of compound 133. Synthesis of compound 133 was completed as described for compound 68 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 395.55, Found 363.3, 396.3 (M-NHOH, M+H).

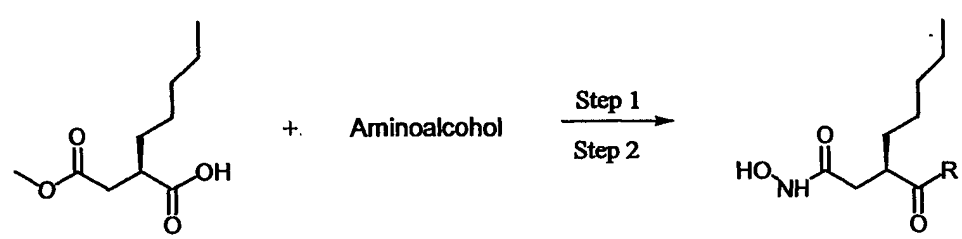
Synthesis of compound 134. Synthesis of compound 134 was completed as described for compound 69 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 383.49, Found 351.2, 384.2 (M-NHOH, M+H).

Synthesis of compound 135. Synthesis of compound 135 was completed as described for compound 70 above for using Boc-isonipecotic acid in place of Boc-thioproline. Calculated weight 411.55, Found 379.2, 412.3 (M-NHOH, M+H).

Synthesis of compound 136. Synthesis of compound 136 was completed as described for compound 71 above for using Boc-isonipacotic acid in place of Boc-thioproline. Calculated weight 399.56, Found 367.3, 400.2 (M-NHOH, M+H).

5:5.8 <u>Aminoalcohol Series</u>

Synthesis of aminoalcohol series of compounds was completed as described below using the following 7 amines: 2-piperidinemethanol, 4-piperidineethanol, N-benzylethanolamine, diethanolamine, N-methylhomoveratrylamine, 2-(methylamino)ethanol, 3-aminobenzyl alcohol, 4-aminophenylethyl alcohol. See Scheme VII below and Table 11 for representative R groups.



Scheme VII

<u>Step 1:</u>

Amines (0.18 mmol) were added to each vial in a 4 x 6 array of tubes. To each was added 0.6 ml of DMF, DIEA (0.091 ml, 0.525 mmol), and chlorotrimethylsilane (0.040 ml, 3.15 mmol), and the array was shaken for 2.5 h.

To a separate solution of (R) methyl (2-pentyl)succinate mono acid (1.0 g, 5.0 mmol) in DMF (14 ml) at 0°C was added EDC (0.96 g, 5.0 mmol) and DIEA (209 ml, 1.2 mmol). This mixture was stirred for 20 min, and aliquots (0.42 ml, 0.15 mmol activated acid) were added to each vial in the amine array, followed by a catalytic amount (ca. 5 mg) of DMAP. The mixtures were shaken for 18 h, diluted with 3 ml ethyl acetate, washed with 10% $NaHSO_4$ (aq) and brine, filtered through Na_2SO_4 and evaporated. The resulting methyl esters were placed in a vacuum chamber under high vacuum overnight, weighed, and analyzed by HPLC/MS.

Step 2:

A methanolic solution of NH_2OH HCl (2 M, 15 ml) was cooled to 0°C. A methanolic solution of KOH (3 M, 15 ml) was added and the mixture was stirred for 30 min and filtered. An aliquot (2 ml, 2.0 mmol NH_2OH) of this solution was added to each of the reaction vials containing the methyl ester product of the previous reaction. The array was shaken for 30 min and Dowex acidic resin (220 mg, 1.125 mmol) was added to each vial and the solutions were filtered, evaporated and purified by preparative HPLC. The product-containing fractions were collected, evaporated in a Savant evaporating centrifuge, and re-analyzed by HPLC/MS.

Synthesis of compound 201: Calculated weight 330.40, Found 268.2, 301.2, 323.2 (M-NHOH, M+H, M+Na)

Synthesis of compound 202: Calculated weight 314.43, Found 282.3, 315.2, 338.2 (M-NHOH, M+H, M+Na)

Synthesis of compound 203: Calculated weight 336.43, Found 304.2, 337.1, 359.0 (M-NHOH, M+H, M+Na)

Synthesis of compound 204: Calculated weight 290.36, Found 258.1, 291.3, 313.2 (M-NHOH, M+H, M+Na)

Synthesis of compound 210: Calculated weight 380.48, Found 348.3, 381.3, 403.2 (M-NHOH, M+H, M+Na)

Synthesis of compound 211: Calculated weight 260.33, Found 228.2, 261.2, 283.2 (M-NHOH, M+H, M+Na)

Synthesis of compound 212: Calculated weight 308.38, Found 276.1, 309.2, 331.1 (M-NHOH, M+H, M+Na)

Synthesis of compound 213: Calculated weight 322.40, Found 290.3, 323.3, 345.1 (M-NHOH, M+H, M+Na)

Piperazine Series I

See Scheme VIII below. See Table 11 for representative R groups.

Step 1:

Synthesis of compound 217. To a stirred solution of piperazine (6.1 g, 71 mmol) in CH_2Cl_2 (50 ml) was added a solution of benzoyl chloride(1.0 g, 7 mmol) in CH_2Cl_2 (50 ml) at 0°C. The reaction mixture was stirred overnight. After addition of H_2O, the mixture was extracted with $CHCl_3$, washed with H_2O, then dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography eluting with $CHCl_3$ / MeOH gave benzoyl piperazine (393 mg).

Step 2 :

To a mixture of (R)-tert-butyl (2-penty)succinate mono N-hydroxysuccinimide ester (500mg, 1.5mmol), benzoylpiperazine (380mg, 2.0 mmol) in CH_2Cl_2 (5.3 ml) was added Et_3N (278 ml, 2.0 mmol) at 0°C. The resulting mixture was stirred at room temperature for 2.5 days, then concentrated and diluted with EtOAc. The organic phase was successively washed with 1N HCl, saturated $NaHCO_3$, brine, and then dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography eluting with n-Hexane / EtOAc gave the 4-((R)-tert-butyl (2-pentyl)succinate) benzoyl piperazine (383 mg).

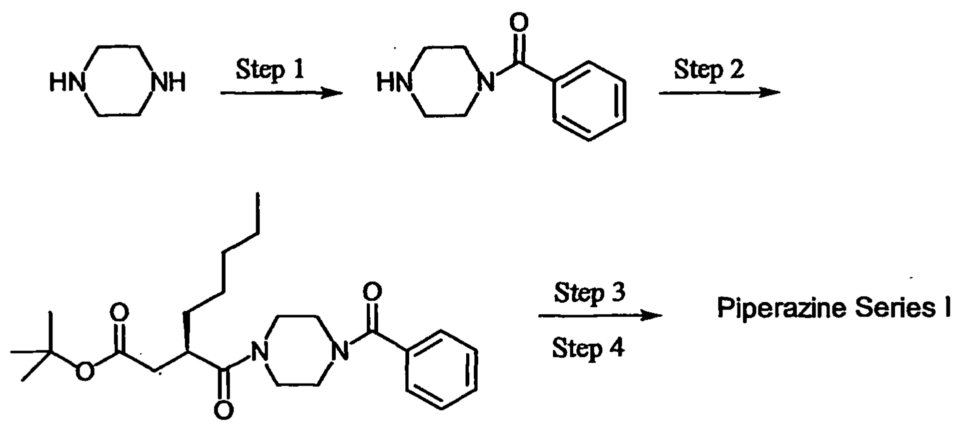
Step 3:

The 4-((R)-tert-butyl (2-pentyl)succinate) benzoyl piperazine (378 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (4 ml) and trifluoroacetic acid (1.6 ml) was added at 0°C. The reaction mixture was stirred at room temperature for 3 h and concentrated. After addition of H_2O, the mixture was extracted with CH_2Cl_2, dried($MgSO_4$) and concentrated to give the acid (193mg).

Step 4:

To a stirring solution of the acid (190 mg, 0.53 mmol), and Et_3N (96 ml, 0.69 mmol) in THF (8 ml) was added isobutyl chloroformate (82 ml, 0.63 mmol) at 0°C. The mixture was stirred at 0°C for 15 min. $TMSONH_2$ was then added and allowed to stir for 2 h. EtOAc was added to the solution and washed with saturated NH_4Cl. The mixture was dried ($MgSO_4$) and concentrated. Purification of the residue was accomplished by

chromatography with the eluants EtOAc then $CHCl_3$/MeOH (10:1) and gave compound 217 (97 mg). Analyzed by [1]H NMR (DMSO-d6) δ: 10.46 (s, 1H), 8.77 (s, 1H), 7.6-7.45 (m, 5H), 3.9-3.1 (m, 9H), 2.34 (dd, J=14.4Hz, 8.4 Hz, 1H), 2.12 (dd, J=15.0Hz, 6.0Hz, 1H), 1.63-1.2 (m, 8H), 1.0-0.85 (m, 3H). HPLC/MS. Calculated weight 375.47, Found 374.2 (M-H).



Scheme VIII

Synthesis of compound 218.

Piperazine series II

See Scheme IX. See table 11 for representative R groups.

Step 1:

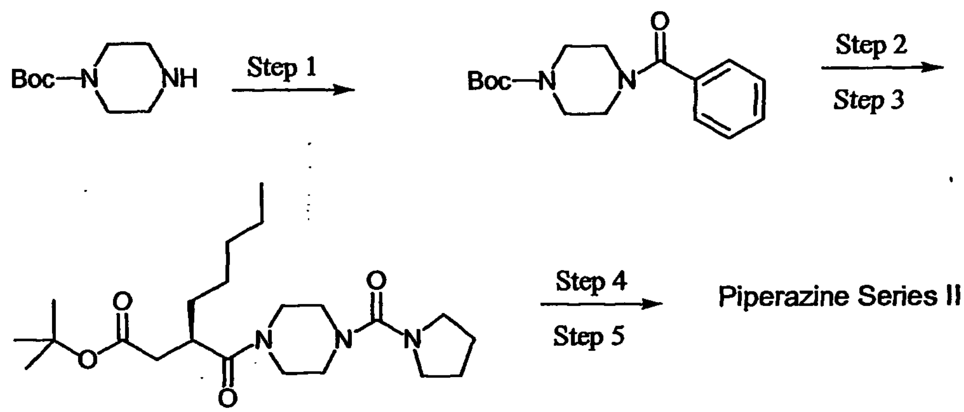
To a stirred solution of Boc-piperazine (1.5 g, 8.1 mmol) and Et_3N (0.9 g, 8.9 mmol) in CH_2Cl_2 (20 ml) was added 1-pyrrolidinecarbonyl chloride (0.89 ml, 8.1 mmol) at 0°C and stirred at room temperature for 3 days. After addition of H_2O, the mixture was extracted with CH_2Cl_2, washed with H_2O, then dried ($MgSO_4$) and concentrated. Purification of the residue was accomplished by chromatography with the eluant EtOAc/n-Hexane (1:10 to 1:2) to give the Boc protected urea (2.18 g).

Step 2:

The Boc protected urea (1.0 g, 3.5 mmol) was dissolved in CH_2Cl_2 (10 ml) and TFA (4 ml) was added at 0°C. The reaction mixture was stirred overnight at room temperature and concentrated. 10% NaOH was added and the pH of the mixture was brought to 10. The mixture was extracted with $CHCl_3$, dried ($MgSO_4$) and concentrated to give the urea (193 mg).

Steps 3-5:

Steps 3-5 in the synthesis of compound 218 were completed as described above in Step 2-4 for the synthesis of compound 217 using the urea from step 2 in place of N-benzoylpiperazine. Analyzed by ^{1}H NMR (DMSO-d6) δ: 10.45 (s, 1H), 8.77 (s, 1H), 4.1-2.7 (m, 13H), 2.32 (dd, J=14.7 Hz, 8.1 Hz, 1H), 2.10 (dd, J=14.7 Hz, 5.9 Hz, 1H), 1.9-1.75 (m, 4H), 1.6-1.1 (m, 8H), 0.97-0.85 (m, 3H). HPLC/MS. Calculated weight 368.48. Found 336.4, 369.4, 391.2 (M-NHOH, M+H, M+Na).



Scheme IX

Aminopyrrolidine

See Scheme X. See Table 11 for representative R groups.

Step1:

Step 1 was completed as described above in Step 1 for the synthesis of compound 217 using (3S)-(+)-1-benzyl-3-amino pyrrolidine in place of piperazine.

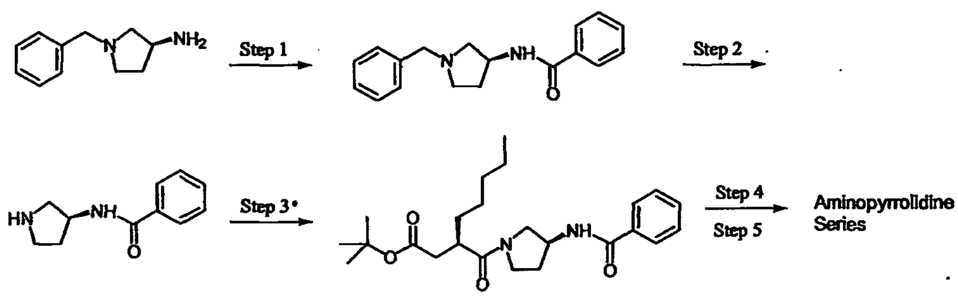
Step 2:

(3S)-1-benzyl-3-(N-benzoylamino) pyrrolidine (400 mg, 1.4 mmol) was dissolved in MeOH (6 ml) and 10% Pd/C (400 mg) was added at 0°C. After addition of HCO_2NH_4 (450 mg, 7.1 mmol), the reaction mixture was heated under reflux for 10 min. The catalyst was filtered off and the filtrate was concentrated to give (3S)- 3-(N-benzoylamino) pyrrolidine (180 mg). MS (ES) 191.3 (M+H)

Steps 3-5:

Steps 3-5 in the synthesis of compound 219 were completed as described above in Step 2-4 for the synthesis of compound 217 using (3S)- 3-(N-benzoylamino) pyrrolidine in place of N-benzoylpiperazine. Analyzed by ^{1}H NMR (DMSO-d6) δ: 10.55-10.45 (m, 1H), 8.8 (s, 1H), 8.65-8.5 (m, 1H), 8.0-7.5 (m, 5H), 4.6-4.45 (m, 1H), 4.0-3.8 (m, 1H), 3.8-3.35

(m, 3H), 3.05-2.8 (m, 1H), 2.4-1:8 (m, 5H), 1.6-1.0 (m, 8H), 0.95-0.75 (m, 3H). HPLC/MS Calculated weight 375.47, Found 343.4, 376.3, 398.2 (M-NHOH, M+H, M+Na).



Scheme X

Hydroxyazetidine Series

See Scheme XI. See Table 11 for representative R groups.

Step 1:

Synthesis of compound 221. Step 1 was completed as described above in Step 2 of the synthesis of compound 219 using 1-diphenyl-3-hydroxyazetidine in place of (3S)-1-benzyl-3-(N-benzoylamino) pyrrolidine.

Step 2:

Step 2 was completed as described above in Step 3 of the synthesis of compound 218 using 3-hydroxyazetidine in place of benzoylpiperazine.

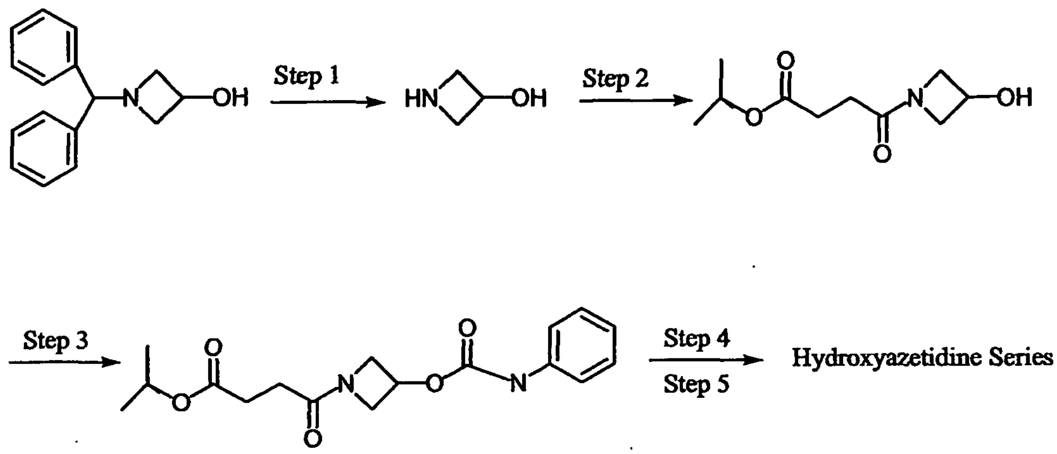
Step 3:

A mixture of the alcohol formed in Step 2 (165 mg, 0.55 mmol), phenyl isocyanate (72 ml, 0.66 mmol), Et_3N (154 ml, 1.10 mmol), DMAP (8 mg, 0.07 mmol) in THF (8 ml) was stirred at 70°C for overnight. EtOAc was added and washed with 1N HCl, saturated Na_2CO_3, brine. The organic layer was dried ($MgSO_4$) and concentrated, followed by addition of $PhCH_3$. Precipitate was filtered off and filtrate was concentrated to give crude (R)-tert-butyl (2-pentyl)succinate amide (250 mg), which was used without further purification.

Steps 4-5:

Steps 4-5 in the synthesis of compound 221 were completed as described above in Step 3-4 for the synthesis of compound 218 using the (R)-tert-butyl (2-penty)succinate amide in place of N-benzoylpiperazine. Analyzed by ^1H NMR (DMSO-d6) δ: 10.45, 10.43 (2s, 1H), 9.96 (s, 1H), 8.8, 8.76 (2s, 1H), 7.6-7.4 (m, 2H), 7.4-7.25 (m, 2H), 7.0-7.1 (m, 1H), 5.3-5.1 (m, 1H), 4.7-4.45 (m, 1H), 4.35-4.0 (m, 2H), 3.9-3.7 (m, 1H), 2.75-2.6

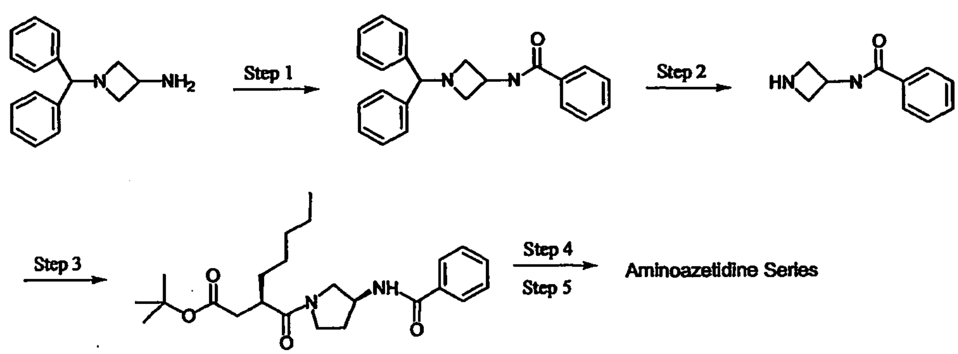
(m, 1H), 2.33-2.13 (m, 1H), 2.13-1.97 (m, 1H), 1.55-0.95 (m, 8H), 0.95-0.8 (m, 3H). HPLC/ MS. Calculated weight 377.44. Found 345.3, 378.3 (M-NHOH, M+H).



Scheme XI

Aminoazetidine

Synthesis of compound 222 was completed as described above for compound 219 using 1 diphenylmethyl-3-amino azetidine in place of (3S)-(+)-1-benzyl-3-amino pyrrolidine. See Scheme XII. Analyzed by ^{1}H NMR (DMSO-d6) δ: 9.1 (br s, 1H), 8.1-7.8 (m, 2H), 7.7-7.4 (m, 3H), 4.85-3.0 (m, 4H), 2.9-1.9 (m, 4H), 1.6-1.0 (m, 8H), 1.0-0.75 (m, 3H). HPLC/ MS. Calculated weight 361.44. Found 329.2, 362.3 (M-NHOH, M+H).



Scheme XII

5.6.1 Synthesis of Related Deformylase Inhibitors

Compounds represented by the Formulas I and II are synthesized as described in section 5.6.1. See Scheme XIII for a general synthetic scheme and Table 11 for representative R groups. Boc-protected amino acids from the group comprising Val, Nva, Phe, Met, Ser(OBn), and Tyr(OBn) were individually treated with amine reagents in the presence of EDC to afford Boc-protected amino amides. Deprotection of the Boc group followed by addition of (R)-tert-butyl (2-pentyl)succinate mono acid and EDC afforded tert-butyl ester substituted amides. Conversion of the tert-butyl esters to the carboxylic acids with subsequent treatment with trimethylsilyldiazomethane afforded the methyl ester. Finally, addition of hydroxylamine hydrochloride yielded the desired products.

Step 1:

Six Boc-protected amino acids (Val, Nva, Phe, Met, Ser(OBn), Tyr(OBn)) were each dissolved in DCM to give a concentration of 1 M, and 4 aliquots (0.48 ml, 0.48 mmol) of each were added to each column of the array, one per vial. Three of the starting amine reagents (pyrrolidine, piperidine, and benzylamine) were each dissolved in DCM at 2.0 M. Dimethylamine was used as provided, in a 2 M THF solution (Aldrich). Six aliquots (0.30 ml, 0.6 mmol) of each of the 4 amine solutions were added to each row of the array, one per vial. A 0.25 M solution of EDC in DCM was prepared and an aliquot (2.40 ml, 0.6 mmol) was added to each vial. The vials were sealed in the block and agitated at 200 rpm on a rotary shaker for 18 h. To each vial was added 1.5 ml 10% $NaHSO_4$ (aq), the array was sealed with the membrane, agitated, and the aqueous layers were withdrawn. The wash procedure was repeated with 10% $NaHSO_4$, $NaHCO_3$ (saturated), and brine. The solutions were filtered through approximately 0.5 g anhydrous Na_2SO_4 each and evaporated to dryness. The resulting Boc-protected amides (oils and solids) were placed in a vacuum chamber under high vacuum overnight, weighed, and analyzed by HPLC/MS.

Step 2:

Deprotection of the Boc-protected amino amides was accomplished by dissolving each product in 2 ml of 4 M HCl in dioxane, followed by shaking for 45 min, and evaporation of solvents. The vials were then placed under high vacuum overnight, weighed, and the amine hydrochlorides were analyzed by HPLC/MS.

Step 3:

To each of the amine hydrochlorides was added a solution of (R) tert-butyl (2-pentyl)succinate mono acid in DCM (2.0 M, 0.20 ml, 0.40 mmol), EDC in DCM (0.25 M, 2.4 ml, 0.60 mmol), and DIEA (209 ml, 1.2 mmol). The mixtures were agitated for 18 h, washed twice with 10% $NaHSO_4$ (aqueous), once each with $NaHCO_3$ (saturated), and

brine, filtered through Na_2SO_4 and evaporated. The resulting tert-butyl ester substituted amides were then weighed and analyzed by HPLC/MS.

Step 4:

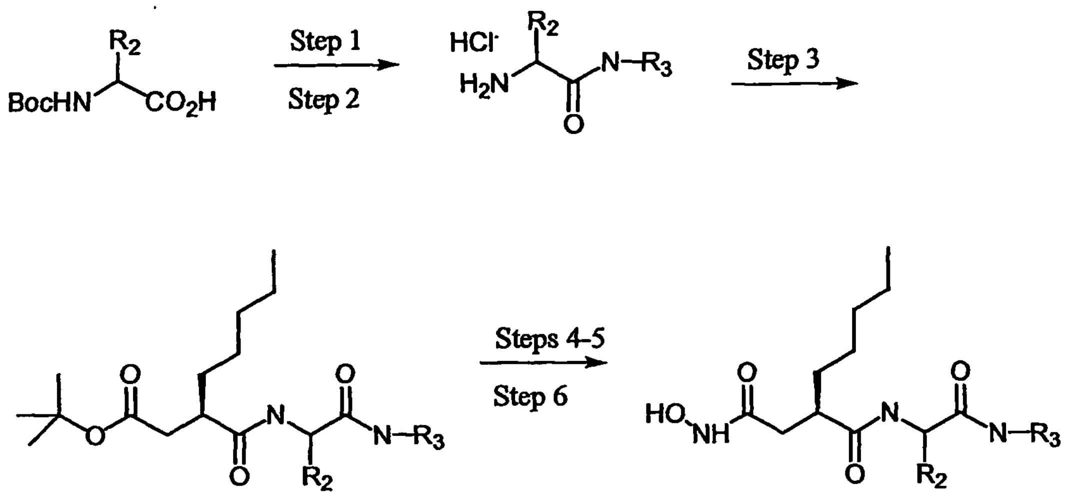
The tert-butyl esters were converted to the carboxylic acids by dissolving each in 2 ml of 4 M HCl in dioxane, shaken for 45 min, and evaporated. The vials were then placed under high vacuum overnight, weighed, and the acids were analyzed by HPLC/MS.

Step 5:

To convert the acids to the corresponding methyl esters each was dissolved in 0.3 ml of methanol and 0.7 ml of benzene, and trimethylsilyldiazomethane in hexanes (2.0 M, 0.60 ml, 1.2 mmol) was added slowly. The array was agitated for 2 h, the solutions were evaporated, and the residues placed under high vacuum overnight. The resulting methyl esters were weighed and analyzed by HPLC/MS.

Step 6:

A methanolic solution of NH_2OH HCl (2 M, 30 ml) was cooled to 0°C. A methanolic solution of KOH (3 M, 30 ml) was added dropwise over 30 min, the mixture was stirred for 30 min and filtered. An aliquot (2 ml, 2.0 mmol NH_2OH) of this solution was added to each of the reaction vials containing the methyl ester product of the previous reaction. The array was agitated for 30 min. Each solution was partially neutralized with 0.10 ml of conc. HCl, then quickly buffered with 0.30 ml of 1 M triethylammonium bicarbonate (pH 7). The solutions were then filtered and directly purified by preparative HPLC. The product-containing fractions were collected, evaporated in a Savant evaporating centrifuge, and re-analyzed by HPLC/MS.



Scheme XIII

Synthesis of compound 137 was accomplished as described in the Section 5.6 calculated M.W. 355.48 found M.W. (M-NHOH, M+H, M+Na) 323.1, 356.3, 378.2.

Synthesis of compound 138 was accomplished as described in the Section 5.6 calculated M.W. 329.44 found M.W. (M-NHOH, M+H, M+Na) 297.1, 330.2, 352.2.

Synthesis of compound 139 was accomplished as described in the Section 5.6 calculated M.W. 377.48 found M.W. (M-NHOH, M+H, M+Na) 345.1, 378.2, 400.1.

Synthesis of compound 140 was accomplished as described in the Section 5.6 calculated M.W. 361.51 found M.W. (M-NHOH, M+H, M+Na) 329.1, 362.1, 384.1.

Synthesis of compound 141 was accomplished as described in the Section 5.6 calculated M.W. 407.51 found M.W. (M-NHOH, M+H, M+Na) 375.2, 408.3, 430.2.

Synthesis of compound 142 was accomplished as described in the Section 5.6 calculated M.W. 483.61 found M.W. (M-NHOH, M+H, M+Na) 451.2, 484.2, 506.2.

Synthesis of compound 143 was accomplished as described in the Section 5.6 calculated M.W. 355.48 found M.W. (M-NHOH, M+H, M+Na) 323.1, 356.3, 378.3.

Synthesis of compound 144 was accomplished as described in the Section 5.6 calculated M.W. 403.52 found M.W. (M-NHOH, M+H, M+Na) 371.2, 404.2, 426.2.

Synthesis of compound 145 was accomplished as described in the Section 5.6 calculated M.W. 387.54 found M.W. (M-NHOH, M+H, M+Na) 355.1, 388.1, 410.1.

Synthesis of compound 146 was accomplished as described in the Section 5.6 calculated M.W. 433.55 found M.W. (M-NHOH, M+H, M+Na) 401.2, 434.2, 456.1.

Synthesis of compound 149 was accomplished as described in the Section 5.6 calculated M.W. 369.50 found M.W. (M-NHOH, M+H, M+Na) 337.2, 370.2, 393.2.

Synthesis of compound 150 was accomplished as described in the Section 5.6 calculated M.W. 417.55 found M.W. (M-NHOH, M+H, M+Na) 385.2, 418.2, 440.2.

Synthesis of compound 151 was accomplished as described in the Section 5.6 calculated M.W. 401.57 found M.W. (M-NHOH, M+H, M+Na) 369.1, 402.2, 424.2.

Synthesis of compound 152 was accomplished as described in the Section 5.6 calculated M.W. 447.58 found M.W. (M-NHOH, M+H, M+Na) 415.3, 448.23, 470.2.

Synthesis of compound 153 was accomplished as described in the Section 5.6 calculated M.W. 523.67 found M.W. (M-NHOH, M+H, M+Na) 491.2, 524.3, 546.3.

Synthesis of compound 154 was accomplished as described in the Section 5.6 calculated M.W. 391.51 found M.W. (M-NHOH, M+H, M+Na) 359.2, 392.3, 414.2.

Synthesis of compound 155 was accomplished as described in the Section 5.6 calculated M.W. 391.51 found M.W. (M-NHOH, M+H, M+Na) 359.2, 392.3, 414.2.

Synthesis of compound 156 was accomplished as described in the Section 5.6 calculated M.W. 439.55 found M.W. (M-NHOH, M+H, M+Na) 407.3, 440.2, 462.2.

Synthesis of compound 157 was accomplished as described in the Section 5.6 calculated M.W. 423.58 found M.W. (M-NHOH, M+H, M+Na) 391.1, 424.1, 446.1.

Synthesis of compound 158 was accomplished as described in the Section 5.6 calculated M.W. 469.58 found M.W. (M-NHOH, M+H, M+Na) 437.2, 470.2, 492.3.

Synthesis of compound 159 was accomplished as described in the Section 5.6 calculated M.W. 545.68 found M.W. (M-NHOH, M+H, M+Na) 513.3, 546.3, 568.3.

Synthesis of compound 161 was accomplished as described in the Section 5.6 calculated M.W. 258.36 found M.W. (M-NHOH, M+H, M+Na) 226.36, 258.2, 281.4.

Synthesis of compound 162 was accomplished as described in the Section 5.6 calculated M.W. 272.39 found M.W. (M-NHOH, M+H, M+Na) 240.4, 273.4, 295.4.

Synthesis of compound 163 was accomplished as described in the Section 5.6 calculated M.W. 256.35 found M.W. (M-NHOH, M+H, M+Na) 224.4, 257.4, 279.2.

Synthesis of compound 164 was accomplished as described in the Section 5.6 calculated M.W. 270.37 found M.W. (M-NHOH, M+H, M+Na) 238.4, 271.4, 293.4.

Synthesis of compound 165 was accomplished as described in the Section 5.6 calculated M.W. 282.34 found M.W. (M-NHOH, M+H, M+Na) 250.3, 283.2, 305.2.

Synthesis of compound 166 was accomplished as described in the Section 5.6 calculated M.W. 336.47 found M.W. (M-NHOH, M+H, M+Na) 304.4, 337.4, 359.4.

Synthesis of compound 167 was accomplished as described in the Section 5.6 calculated M.W. 278.35 found M.W. (M-NHOH, M+H, M+Na) 246.3, 279.2, 301.2.

Synthesis of compound 168 was accomplished as described in the Section 5.6 calculated M.W. 363.46 found M.W. (M-NHOH, M+H, M+Na) 331.3, 364.4, 386.3.

Synthesis of compound 169 was accomplished as described in the Section 5.6 calculated M.W. 364.49 found M.W. (M-NHOH, M+H, M+Na) 332.4, 365.3, 387.2.

Synthesis of compound 170 was accomplished as described in the Section 5.6 calculated M.W. 296.34 found M.W. (M-NHOH, M+H, M+Na) 264.2, 297.2, 319.2

Synthesis of compound 171 was accomplished as described in the Section 5.6 calculated M.W. 357.25 found M.W. (M-NHOH, M+H, M+Na) 381.0, (Br isotopes) 324.2, 326.2, 357.2, 359.2, 379.0, 381.0.

Synthesis of compound 172 was accomplished as described in the Section 5.6 calculated M.W. 357.25 found M.W. (M-NHOH, M+H, M+Na) (Br isotopes) 324.2, 326.2, 357.2, 359.2, 379.0, 381.0.

Synthesis of compound 173 was accomplished as described in the Section 5.6 calculated M.W. 312.80 found M.W. (M-NHOH, M+H, M+Na) (Cl isotopes) 280.2, 282.1, 313.3, 315.2, 335.2, 337.2.

Synthesis of compound 174 was accomplished as described in the Section 5.6 calculated M.W. 338.40 found M.W. (M-NHOH, M+H, M+Na) 306.2, 339.3, 361.2.

Synthesis of compound 173 was accomplished as described in the Section 5.6 calculated M.W. 370.45 found M.W. (M-NHOH, M+H, M+Na) 338.3, 371.2, 393.2.

Synthesis of compound 176 was accomplished as described in the Section 5.6 calculated M.W. 370.45 found M.W. (M-NHOH, M+H, M+Na) 338.2, 371.3, 393.3.

Synthesis of compound 177 was accomplished as described in the Section 5.6 calculated M.W. 335.40 found M.W. (M-NHOH, M+H, M+Na) 303.2, 336.2, 358.2.

Synthesis of compound 183 was accomplished as described in the Section 5.6 calculated M.W. 398.55 found M.W. (M-NHOH, M+H, M+Na) 399.4

Synthesis of compound 184 was accomplished as described in the Section 5.6 calculated M.W. 349.43 found M.W. (M-NHOH, M+H, M+Na) 317.4, 350.4, 372.2.

Synthesis of compound 185 was accomplished as described in the Section 5.6 calculated M.W. 420.55 found M.W. (M-NHOH, M+H, M+Na) 421.4.

Synthesis of compound 186 was accomplished as described in the Section 5.6 calculated M.W. 365.43 found M.W. (M-NHOH, M+H, M+Na) 333.3, 366.4.

Synthesis of compound 187 was accomplished as described in the Section 5.6 calculated M.W. 436.55 found M.W. (M-NHOH, M+H, M+Na) 437.3.

Synthesis of compound 188 was accomplished as described in the Section 5.6 calculated M.W. 438.48 found M.W. (M-NHOH, M+H, M+Na) 406.3, 439.2, 461.22.

Synthesis of compound 189 was accomplished as described in the Section 5.6 calculated M.W. 452.51 found M.W. (M-NHOH, M+H, M+Na) 420.2, 453.3.

Synthesis of compound 190 was accomplished as described in the Section 5.6 calculated M.W. 353.39 found M.W. (M-NHOH, M+H, M+Na) 321.12, 353.4.

Synthesis of compound 191 was accomplished as described in the Section 5.6 calculated M.W. 367.42 found M.W. (M-NHOH, M+H, M+Na) 3335.3, 368.4, 390.2.

Synthesis of compound 182 was accomplished as described in the Section 5.6 calculated M.W. 358.48 found M.W. (M-NHOH, M+H, M+Na) 359.3.

Synthesis of compound 178 was accomplished as described in the Section 5.6 calculated M.W. 317.39 found M.W. (M-NHOH, M+H, M+Na) 285.4, 318.3, 340.4.

Synthesis of compound 179 was accomplished as described in the Section 5.6 calculated M.W. 384.52 found M.W. (M-NHOH, M+H, M+Na) 385.4.

Synthesis of compound 180 was accomplished as described in the Section 5.6 calculated M.W. 386.45 found M.W. (M-NHOH, M+H, M+Na) 354.4, 387.4, 409.3.

Synthesis of compound 181 was accomplished as described in the Section 5.6 calculated M.W. 327.42 found M.W. (M-NHOH, M+H, M+Na) 295.4, 328.4, 350.3.

5.6.2 Synthesis of Compounds of Formulas I and II

Compounds represented by Formulas I and II are synthesized as described in section 5.6.2. See Scheme XIV for a general synthetic scheme and Table 11 for representative R groups.

The following series of 24 amines was used: butylamine, amylamine, diethylamine, pyrrolidine, piperidine, morpholine, furfurylamine, Boc-piperizine, 1-adamantylamine, aniline, 4-morpholinoaniline, 4-pentyloxyaniline, 2-fluoroaniline, 3-fluoroaniline, 4-fluoroaniline, 3-bromoaniline, 4-bromoaniline, 4-chloroaniline, 3,5-dimethoxyaniline, 3-phenoxyaniline, 4-phenoxyaniline, 3-aminobenzamide, 4-aminobenzamide, 4-aminoacetanilide.

Step 1:

The series of 24 amines was added to each vial in a 4 x 6 array of tubes. To each was added 1 ml of DCM and a solution of (R) tert-butyl (2-pentyl)succinate mono N-hydroxysuccinimide ester in DCM (0.25 M, 1.20 ml, 0.30 mmol). The mixtures were agitated for 18 h, diluted to 2.5 ml with DCM, washed twice with 10% $NaHSO_4$ (aqueous), once each with $NaHCO_3$ (saturated), and brine, filtered through Na_2SO_4 and evaporated. The resulting tert-butyl ester substituted amides were then weighed and analyzed by HPLC/MS.

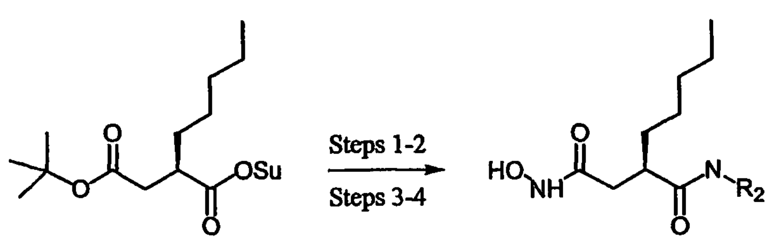
Small amounts of unreacted succinate-NHS ester from the mixtures were removed by diluting with 1 ml of DCM and approximately 50 mg of tris(2-aminoethyl)amine, polymer-bound (4.4 mmol N/g, Aldrich) was added. The mixtures were agitated for 18 h, filtered, evaporated, and analyzed by HPLC/MS.

Step 2:

The tert-butyl esters were converted to the carboxylic acids by dissolving each in 2 ml of a solution of 100:5:1 TFA:water:DMS, followed by shaking for 45 min, and evaporation of solvents. The vials were then placed under high vacuum overnight, weighed, and the acids were analyzed by HPLC/MS.

Steps 3-4:

Performed as in steps 5 and 6 in Section 5.6.1, as described above.



Scheme XIV

5.6.3 Synthesis of Compounds of Formulas I and II

Compounds represented by Formulas I and II are synthesized as described in section 5.6.3. See Scheme XIV for a general synthetic scheme and Table 11 for representative R groups.

These compounds were synthesized in a procedure similar to the above series, except that 0.36 mmol of Boc-protected amino acid starting materials were used and all other reagents were scaled appropriately. Also, N-hydroxysuccinimide (NHS) esters were used as coupling partners in Step 1 and Step 3 instead of the free acids and EDC.

Step 1:

Six Boc-protected amino acid NHS esters (Gly, b-Ala, Lys(Z), Ser(OBn), Asp(OBn, Glu(OBn)) were each dissolved in DCM to a concentration of 0.75 M, and 4 aliquots (0.48 ml, 0.36 mmol) of each were added to each column of the array, one per vial. Three of the starting amine reagents (pyrrolidine, piperidine, and benzylamine) were each dissolved in DCM at 2.0 M. Dimethylamine was used as provided, in a 2 M THF solution (Aldrich). Six aliquots (0.225 ml, 0.45 mmol) of each of the 4 amine solutions were added to each row of the array, one per vial. The mixtures were agitated for 18 h, washed twice with 10% $NaHSO_4$ (aqueous), once each with $NaHCO_3$ (saturated), and brine, filtered through Na_2SO_4 and evaporated. The resulting Boc-protected amides (oils and solids) were placed in a vacuum chamber under high vacuum overnight, weighed, and analyzed by HPLC/MS.

Step 2:

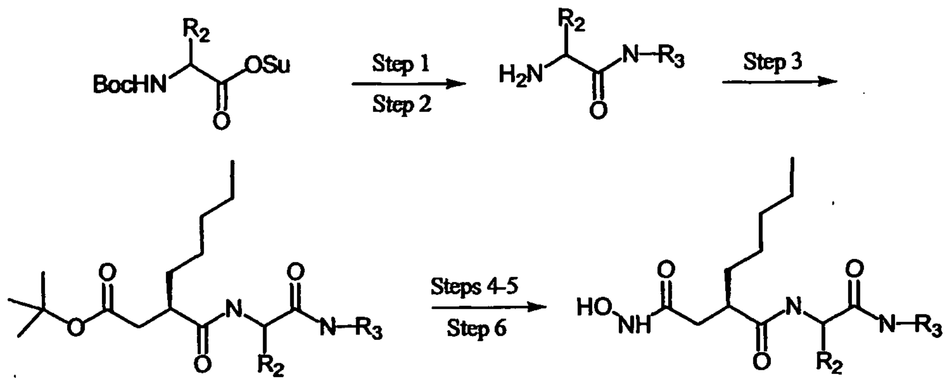
Performed as in Step 2 of Section 5.6.2, as described above.

Step 3:

To each of the amine hydrochlorides from Step 2 was added a solution of (R) tert-butyl (2-pentyl)succinate mono N-hydroxysuccinimide ester in DCM (1.5 M, 0.20 ml, 0.30 mmol), and DIEA (209 ml, 1.2 mmol). The mixtures were agitated for 18 h, washed twice with 10% $NaHSO_4$ (aq), once each with $NaHCO_3$ (saturated), and brine, filtered through Na_2SO_4 and evaporated. The resulting tert-butyl ester substituted amides were then weighed and analyzed by HPLC/MS.

Steps 4-6:

Performed as in steps 4-6 of Section 5.6.2, as described above.



Scheme XV

5.6.4 Synthesis of Compounds of Formulas I and II

Compounds represented by the Formulas I and II are synthesized as described in section 5.6.4. See Scheme XIII for a general synthetic scheme and Table 11 for representative R groups.

These compounds were synthesized in a procedure similar to the above series, except that the amine reagents used were aniline, p-toluidine, p-anisidine, and p-fluoroaniline.

The group of 24 amines used was: 3-hydroxypiperidine hydrochloride, 4-hydroxypiperidine, 2-piperidinemethanol, 3-piperidinemethanol, 2-piperidineethanol, 4-piperidineethanol, N-benzylethanolamine, diethanolamine, 1-(2-hydroxyethyl)piperazine, N-methylhomoveratrylamine, nipecotamide, 2-(propylamino)ethanol, 2-(methylamino)ethanol, N-methylhydroxylamine hydrochloride, N,O-dimethylhydroxylamine hydrochloride, Boc-piperazine, 2-aminobenzyl alcohol, 3-aminobenzyl alcohol, 4-aminophenylethyl alcohol, N-benzylaspartic acid, DL-proline, isonipecotic acid, nipecotic acid

Step 1:

The series of 24 amines (0.18 mmol) was added to each vial in a 4 x 6 array of tubes. To each was added 0.6 ml of DMF, DIEA (0.091 mL, 0.525 mmol), and chlorotrimethylsilane (0.040 ml, 3.15 mmol), and the array was agitated for 2.5 h.

To a separate solution of (R) methyl (2-pentyl)succinate mono acid (1.0 g, 5.0 mmol) in DMF (14 ml) at 0°C was added EDC (0.96 g, 5.0 mmol) and DIEA (209 ml, 1.2

mmol). This mixture was stirred for 20 min, and aliquots (0.42 ml, 0.15 mmol activated acid) were added to each vial in the amine array, followed by a catalytic amount (ca. 5 mg) of DMAP. The mixtures were agitated for 18 h, diluted with 3 ml ethyl acetate, washed with 10% $NaHSO_4$ (aqueous) and brine, filtered through Na_2SO_4 and evaporated. The resulting methyl esters were placed in a vacuum chamber under high vacuum overnight, weighed, and analyzed by HPLC/MS.

Step 2:

A methanolic solution of NH_2OH HCl (2 M, 15 ml) was cooled to 0°C. A methanolic solution of KOH (3 M, 15 ml) was added and the mixture was stirred for 30 min and filtered. An aliquot (2 ml, 2.0 mmol NH_2OH) of this solution was added to each of the reaction vials containing the methyl ester product of the previous reaction. The array was agitated for 30 min and H+ Dowex (220 mg, 1.125 mmol) was added to each vial and the solutions were filtered, evaporated and purified by preparative HPLC. The product-containing fractions were collected, evaporated in a Savant evaporating centrifuge, and re-analyzed by HPLC/MS.

5.6.5 Synthesis of Compounds of Formula XX

Compounds represented by the following general structure are synthesized as described in section 5.6.5. See Scheme III for a general synthetic scheme and Table 16 for representative R groups.

D-Phenylalanine phenyl amide hydrochloride was prepared from Boc-Phe-NHS by standard procedures. This salt (54 mg, 0.20 mmol) was dissolved in 0.8 ml of DCM containing (R) tert-butyl (2-pentyl)succinate mono N-hydroxysuccinimide ester (740 mg, 0.19 mmol) and DIEA (37 ml, 0.21 mmol). The mixture was stirred at 35 °C for 24 h, diluted with DCM and washed once each with 0.2 M HCL, $NaHCO_3$ (saturated), and brine, filtered through $MgSO_4$, and evaporated. The residue was analyzed by HPLC/MS and NMR and carried on without further purification.

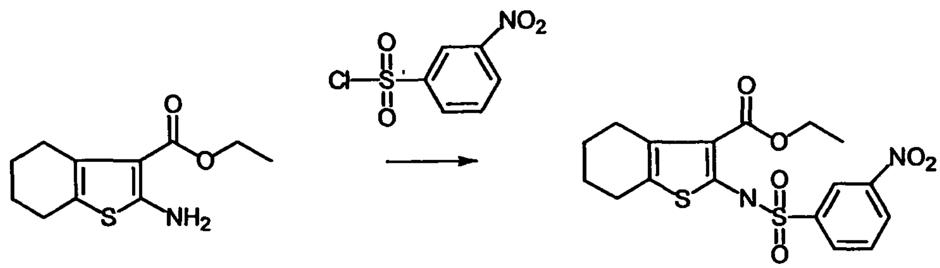
The succinyl tert-butyl ester (64 mg, 0.137 mmol) was dissolved in 1 ml of 100:5:1 TFA:water:DMS, stirred for 30 min, and evaporated. The residue was then dissolved in 2 ml 3:1 benzene:methanol and trimethylsilyldiazomethane in hexanes (2.0 M, 0.50 ml, 1.0 mmol) was added dropwise with stirring. After 20 min the color was discharged by dropwise addition of acetic acid and the solution was evaporated to yield approximately 75 mg of a pale yellow oil which was analyzed by HPLC/MS and carried on without further purification.

A methanolic solution of NH_2OH HCl (2 M, 0.50 ml) was cooled to 0°C. A methanolic solution of KOH (3 M, 0.5 ml) was added and the mixture was stirred for 30 min and filtered. An aliquot (0.35 ml, 0.35 mmol NH_2OH) of this solution was added to a solution of the succinyl methyl ester from the previous reaction (0.137 mmol theoretical) in 0.2 ml MeOH. The mixture was stirred for 30 min and HCl (12 M, 50 ml, 0.69 mmol) was added followed immediately by 100 ml 1 M triethylammonium bicarbonate (pH 7). The mixture was evaporated and purified by preparative HPLC. The product-containing fractions were collected and evaporated, providing 21 mg (36% yield) of the hydroxamic acid. MS (ES), 393.1, 426.2, 448.1 (M-NHOH, M+H, M+Na); ^{1}H NMR (CD3OD) δ 0.93 (t, J = 7.0, 3 H), 1.09-1.49 (m, 8 H), 2.23 (dd, J = 5.1, 15.3, 1 H), 2.33-2.55 (m, 1 H), 2.65-2.78 (m, 1 H), 2.98 (dd, J = 10.9, 14.1, 1 H), 3.50 (dd, J = 4.4, 14.0, 1 H), 4.4.70-4.90 (m, 1 H), 7.15-7.60 (m, 10), 7.79 (d, J = 7.7, 2 H).

5.7.1. Synthesis of Compounds of Formula XVIII

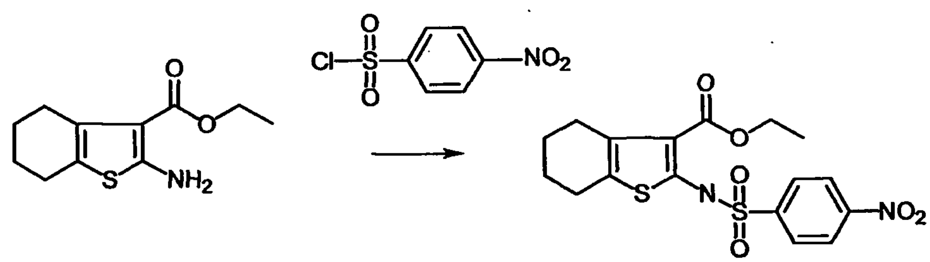
Compounds represented by the Formula XVIII are synthesized as described in section 5.7.1. See Schemes XVI and XVII for general synthetic schemes and Table 14 for representative R groups.

Synthesis of compound 239. A mixture of 2-amino-4,5,6, 7-tetrahydrobenzo[B] thiophene-3-carboxylic acid ethyl ester (200 mg, 0.89 mmol), 3-nitrobenzenesulfonyl chloride (295 mg, 1.33 mmol), and pyridine (4.4 ml) was heated under reflux for 1 h. The reaction mixture was concentrated in vacuo. $CHCl_3$ was added to the residue, then washed with 1 N HCl and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by preparative TLC (EtOAc/n-Hexane, 1:4), and recrystallization (CH_2Cl_2/n-Hexane) to give compound 239 (66 mg). Analyzed by ^{1}H NMR (DMSO-d6) δ: 10.87 (br s, 1H), 8.6-8.5 (m, 2H), 8.23-8.17 (m, 1H), 8.0-7.9 (m, 1H), 4.09 (q, J=7.0 Hz, 2H), 2.7-2.5 (m, 4H), 1.8-1.65 (m, 4H), 1.2 (t, J=7.0 Hz, 3H). HPLC/MS. Calculated weight 410.47. Found 409.0 (M-H).



Scheme XVI

Synthesis of compound 240. Synthesis of compound 240 was completed as described above for compound 239 using 4-nitrobenzenesulfonyl chloride in place of 3-nitrobenzenesulfonyl chloride. See Scheme XVII. Analyzed by ^{1}H NMR (DMSO-d6) δ: 10.88 (br s, 1H), 8.51-8.43 (m, 2H), 8.1-8.02 (m, 2H), 4.12 (q, J=7.0 Hz, 2H), 2.7-2.55 (m, 4H), 1.85-1.65 (m, 4H), 1.22 (t, J=7.0 Hz, 3H). HPLC/MS. Calculated weight 410.47. Found 409.0 (M-H).



Scheme XVII

Synthesis of the NH_2 derivative. To a solution of compound 240 (250 mg, 0.61 mmol) in EtOH (150 ml) was added 10% Pd/C (150 mg) and it was shook 2 h under H_2 at room temperature. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. Recrystallization from $CHCl_3$/EtOH/diisopropyl ether gave the NH_2 derivative (83 mg).

Synthesis of compound 241. The reaction mixture containing -NH_2 derivative (52 mg, 0.14 mmol), acetic anhydride (56 mg, 0.55 mmol), and $CHCl_3$ (1 ml) was stirred overnight at room temperature, and concentrated. The residue was purified by chromatography (EtOAc/n-Hexane, 1:2 to 1:1), and recrystallization (CH_2Cl_2/n-Hexane) to give compound 241 (28 mg). Analyzed by ^{1}H NMR (DMSO-d6) δ: 10.43 (br s, 1H), 10.40 (br s, 1H),

7.84-7.74 (m, 4H), 4.18 (q, J=7.2 Hz, 2H), 2.7-2.55 (m, 4H), 1.82-1.65 (m, 4H), 1.26 (t, J=7.2 Hz, 3H). HPLC/MS. Calculated weight 422.53. Found 377.0, 423.0 (M-EtO, M+H).

Synthesis of compound 242. To a solution of formic acid (19 mg, 0.41 mmol) in $CHCl_3$ (0.5 ml) was added acetic anhydride (41 mg, 0.40 mmol), followed by the -NH_2 derivative (30 mg, 0.08 mmol) . The reaction mixture was stirred 1 h at room temperature, and concentrated. The residue was purified by chromatography (EtOAc/n-Hexane, 1:4 to 1:1), and recrystallization (CH_2Cl_2 / diisopropyl ether) to give compound 242 (7 mg). Analyzed by ^{1}H NMR (DMSO-d6) δ: 10.69 (br s, 1H), 10.46 (br s, 1H), 8.41 (s, 1H), 7.81 (s, 4H), 4.18 (q, J=7.2 Hz, 2H), 2.75-2.5 (m, 4H), 1.87-1.57 (m, 4H), 1.27 (t, J=7.2 Hz, 3H). HPLC/MS. Calculated weight 408.50. Found 363.0, 409.0, 431.0 (M-EtO, M+H, M+Na).

Synthesis of compound 243. The reaction mixture containing the NH_2 derivative (104 mg, 0.27 mmol), methanesulfonyl chloride (80.3 ml, 1.04 mmol), Et_3N (29.3 ml, 0.21 mmol), and pyridine (1 ml) was heated under reflux for 1 h, and then concentrated. The residue was diluted with $CHCl_3$, washed with 1N HCl, dried ($MgSO_4$) and concentrated. Purification by chromatography (EtOAc/n-Hexane, 1:2) and recrystallization (CH_2Cl_2/ diisopropyl ether) gave compound 243 (17 mg). Analyzed by ^{1}H NMR (DMSO-d6) δ: 10.7-10.3 (m, 2H), 7.8 (d, J=9.0 Hz, 2H), 7.38 (d, J=9.0 Hz, 2H), 4.18 (q, J=7.1 Hz, 2H), 3.2 (s, 3H), 2.7-2.5 (m, 4H), 1.88-1.6 (m, 4H), 1.27 (t, J=7.1 Hz, 3H). HPLC/MS. Calculated weight 458.58. Found 457.0 (M-H).

5.7.4 Synthesis of Compounds of Formula XXI

Compounds represented by the following general structure are synthesized as described in section 5.7.4. See Scheme XVIII for general synthetic schemes and Table 18 for representative R groups.

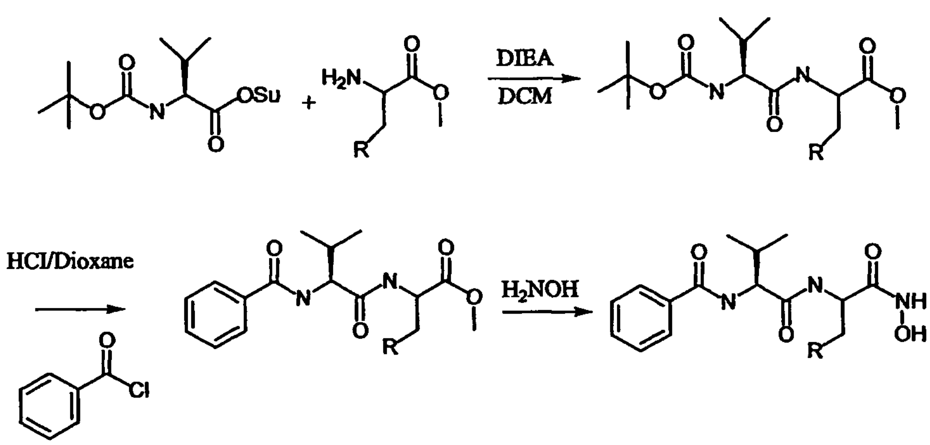
Synthesis of Capped Dipeptide Series

Synthesis of compound 274. Boc-Val-OSu (0.500 g, 1.59 mmol) was added to a solution of H-Nle-OMe.HCl (0.318 g, 1.75 mmol) in DCM (5 ml). DIEA (0.410 g, 0.553 ml, 3.18 mmol) was added and the reaction was shaken overnight. The reaction was diluted with DCM, washed with 5% aqueous citric acid, 5% aqueous K_2CO_3 and brine. The organic

layers were dried over Na_2SO_4 and the solvent removed in vacuo. The residue was treated with 4.0 M HCl/dioxane and again the solvent was removed by vacuum.

The resulting amine was dissolved in DCM (2 ml). DIEA (0.172 g, 0.232 ml, 4.02 mmol) was added followed by the addition of benzoyl chloride (0.198 g, 0.164 ml, 1.41 mmol). The reaction was stirred over night. The reaction was diluted with ether, washed with 5% citric acid, 5% K_2CO_3 and brine. The organic layers were dried over Na_2SO_4, and the solvent removed in vacuo. The residue was purified via flash chromatography to give the methyl ester.

The ester was taken up in a basic solution of hydroxyl amine (1.0 M hydroxylamine; 0.5 M KOH) in MeOH. This was stirred for 15 min and sat. $NaHCO_3$ was added to quench the reaction. The solution was extracted 3 X DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed in vacuo. The residue was purified via flash chromatography to give 0.054 g compound 274 which was analyzed by HPLC/MS. Calculated weight 349.43, Found 348.4 (M-H).



Scheme XVIII

Synthesis of compound 275. Synthesis of compound 275 was completed as described above for compound 274 using D-Boc-Val-OSu in place of Boc-Val-OSu. Analyzed by HPLC/MS. Calculated weight 349.43, Found 348.4 (M-H).

Synthesis of compound 276. Synthesis of compound 276 was completed as described above for compound 274 using H-Cha-Ome .HCl in place of H-Nle-OMe.HCl. Analyzed by HPLC/MS. Calculated weight 389.50, Found 388.2 (M-H).

Additional Capped Dipeptides

See scheme XIX.

Step 1:

To a stirring solution of Boc-Nle-OH (0.7 g, 3 mmol) and triethylamine (0.42 ml, 3 mmol) in 1: 1 THF/Ether (15 ml) was added isobutylchloroformate (0.39 ml, 3 mmol) at -20°C. After stirring for 30 min at -20°C, a diazomethane ethereal solution (30 ml, 0.1 M) was added and allowed to stir at -20°C for 30 min and gradually warm to room temperature. After stirring for 16 h, the solution was quenched with a few drop of acetic acid and poured into ether (30 ml), washed with saturated aqueous $NaHCO_3$ (30 ml) and brine (30 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by flash chromatography (25% EtOAc/Hexane) to provide 0.25 g (34%) of diazoketone as product. Analyzed by ^1H NMR (CDCl3) δ: 0.98 (t, 3H), 1.38 (m, 4H), 1.52 (s, 9H), 1.61 (m, 1H), 1.95 (m, 1H), 4.23 (bs, 1H), 5.18 (d, 1H), 5.55 (s, 1H).

Step 2:

To a stirring solution of diazoketone (0.73 g, 3 mmol) in MeOH (5 ml) at 0°C was added silver benzoate (68 mg, 0.3 mmol) and triethylamine (0.84 ml, 6 mmol). The solution was allowed to stir at 0°C for 2 h then concentrated to dryness. The residue was taken up in EtOAc (30 ml) and washed with H_2O (20ml) and 0.5 N HCl (15 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by flash chromatography (20% EtOAc/Hexane) to provide 0.55 g (72%) of Boc-Nle-methyl ester as product. Analyzed by ^1H NMR (CDCl3) δ: 0.98 (t, 3H), 1.38 (m, 4H), 1.52 (m, 11H), 2.62 (m, 2H), 3.76 (s, 3H), 3.98 (m, 1H), 4.98 (d, 1H).

Steps 3 and 4:

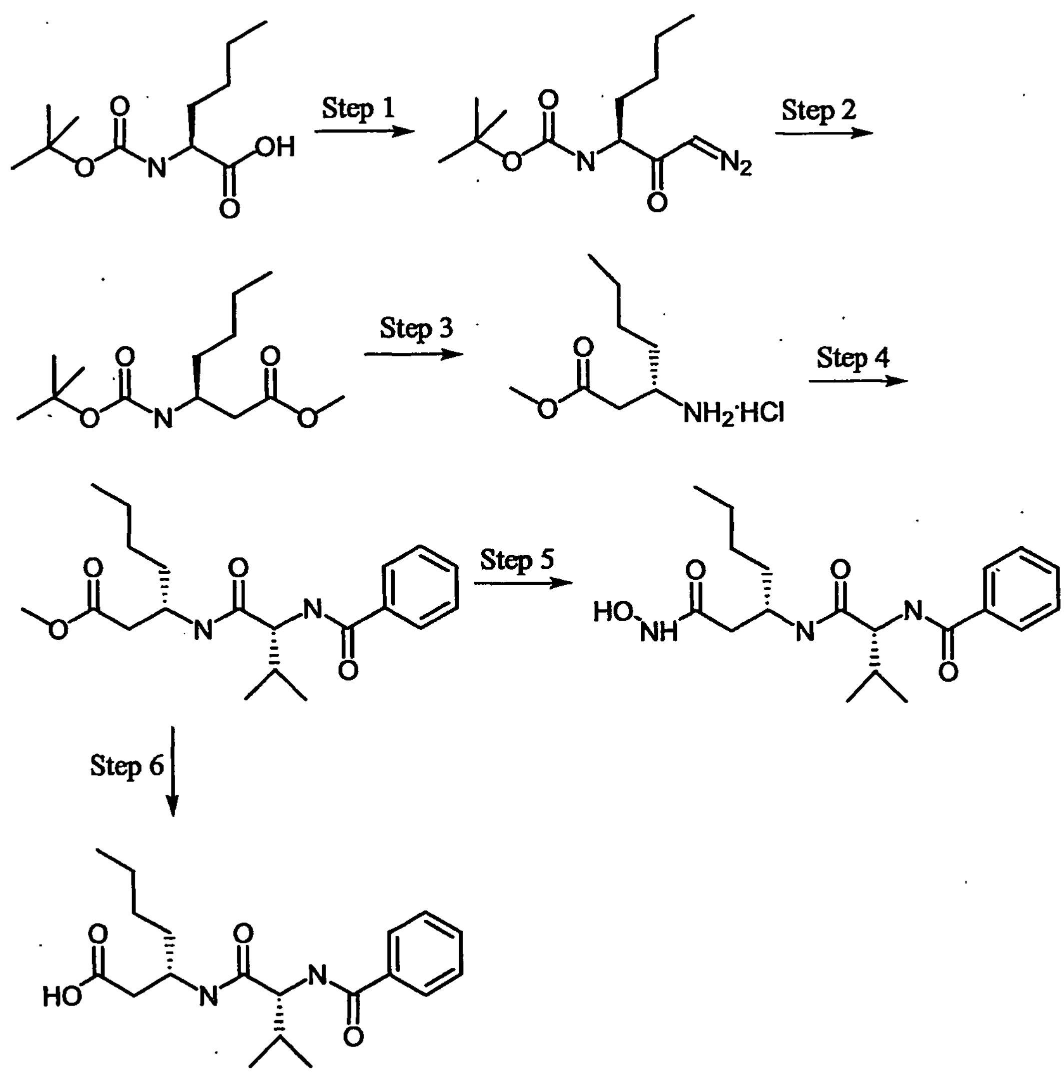
Boc-Nle-methyl ester (0.55g, 2.1 mmol) was treated with 4N HCl/dioxane (2 ml) for 30 min. The solution was concentrated to dryness, yielding 0.43 g of Nle-methyl ester HCl salt which was used in the next step.

A mixture of EDC (130 mg, 0.67 mmol), HOBT (120 mg, 0.89 mmol) and Bz-Val-OH (150 mg, 0.67 mmol) was stirred in DMF (3 ml) for 15 min. At which time, a solution of b-Nle-methyl ester HCl salt (87 mg, 0.45 mmol) in DMF (2 ml) was added followed by the addition of triethylamine (63 ml, 0.45 mmol). The resulting mixture was stirred for 16 h then poured into saturated aqueous ammonium chloride (15 ml) and EtOAc (10 ml). The aqueous layer was separated and extracted with EtOAc (10 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by flash chromatography (40%

EtOAc/Hexane) to provide 130 mg (80%) of the title compound, a mixture of 2 diastereomers. Analyzed by HPLC/MS. Calculated weight 362.47. Found 363.15 (M+H).

Step 5:

A methanolic solution of $NH_2OH.HCl$ (2 M, 5 ml) was cooled to 0°C. A methanolic solution of KOH (3 M, 5 ml) was added dropwise over 10 min, the mixture was stirred for 30 min and filtered. An aliquot (1.5 ml, 1.5 mmol) of this solution was added to the methyl ester (60 mg, 0.16 mmol). The mixture was allowed to stir for 20 min and acidified to pH = 5 by Dowex acidic resin. The solvent was removed and the residue was purified by preparative HPLC to isolated compound 277 and compound 278 (diastereomers) in pure form. Analyzed by HPLC/MS. Calculated weight 363.46. Found 362.15 (M-H).



Scheme XIX

Step 6:

Methyl ester (60 mg, 0.16 mmol) from step 4 was treated with 1M LiOH/MeOH (2 ml) for 18 h. Dowex acidic resin was added to acidify the solution to pH = 5. The filtrate was collected and concentrated to dryness to give 45 mg (79%) of compound 279 as desired product. Analyzed by HPLC/MS. Calculated weight 348.45. Found 347.10 (M-H).

5.7.2 Synthesis of Compounds of Formula XVII

Synthesis of Capped Valine series

Compounds represented by Formulas XVI and XVII are synthesized as described in section 5.7.2 See scheme XX for a general synthetic scheme and Tables 12 and 13 for representative structures.

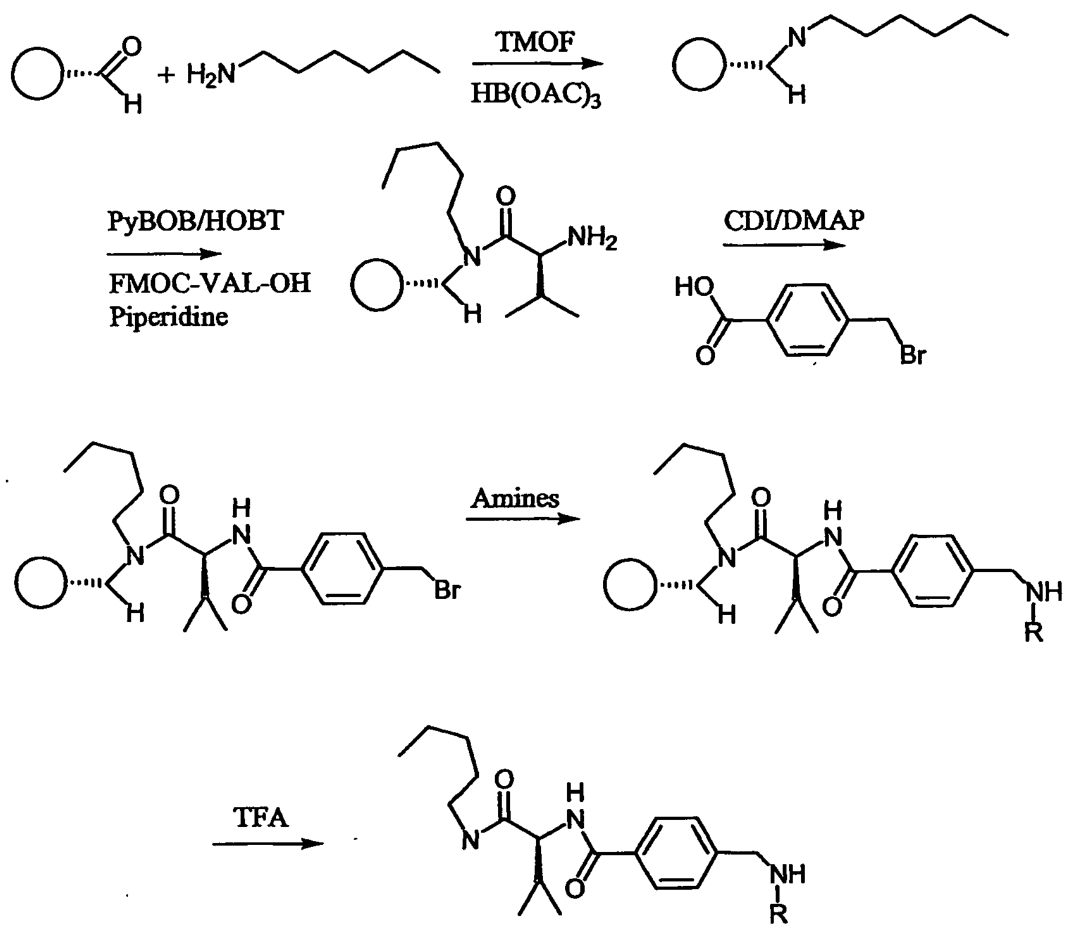
Synthesis of compound 224. Pentylamine (1.31 g, 1.74 ml, 15.0 mmol) was added to a suspension of Argopore MB-CHO resin (1.0 g, 0.75 mmol) in DCM (5 ml) and trimethylorthoformate (5 ml) and shaken for 3 hr. The resin was filtered and washed quickly 3 times with dry DCM. The resin was then suspended in DCM (5 ml). Sodium triacetoxyborohydride (3.18 g, 15 mmol) was then added and the reaction was shaken over night. The resin was then filtered and washed repeatedly (3 X DMF, 1 X DCM, 1 X MeOH, 3 X DCM) and dried by vacuum to give the pentyl amine resin.

A mixture of FMOC-Val-OH (0.764 g, 2.25 mmol), PyBOP (1.17 g, 2.25 mmol) and HOBT (0.304 g, 2.25 mmol) in DCM (5 ml) was shaken for 30 min and added to the pentylamine resin (1 g, 0.75 mmol). This was shaken over night and filtered. The resin was washed (3 X DMF, 1 X DCM, 1 X MeOH, 3 X DCM) and dried in vacuo to give the valine capped pentyl amine resin. This resin was treated for 30 min with 20% piperidine in toluene for 30 minutes, washed repeatedly (3 X DMF, 1 X DCM, 1 X MeOH, 3 X DCM) and dried in vacuo to give the deprotected amino acid bound resin.

Diisopropyl carbodiimide (0.473 g, 0.550 ml, 3.75 mmol) was added to 3-bromomethylbenzoic acid (0.806 mg, 3.75 mmol) and DMAP (0.0046 g, 0.0375 mmol) in DMF (3 ml). This solution was shaken for 5 min and added to the above resin (0.500 g, 0.375 mmol) and shaken over night. The resin was washed repeatedly (3 X DMF, 1 X DCM, 1 X MeOH, 3 X DCM) and dried in by vacuum to give the capped valine resin.

1,2,3,4-Tetrahydro-1-napthylamine (0.057 ml, 0.375 mmol) was added to a suspension of the capped valine resin (0.050 g, 0.0375 mmol) in DMF (1 ml) and shaken overnight. The resin was then filtered and washed repeatedly (3 X DMF, 1 X DCM, 1 X

MeOH, 3 X DCM) to give the compound 224 bound resin. The damp resin was treated with 80% trifluoroacetic acid in DCM for 1 h and filtered. The resin was washed with DCM and the combined filtrate was dried in vacuo to give 4.4 mg of compound 224 which was analyzed by HPLC/MS. Calculated weight 449.64, Found 450 (M+H).



Scheme XX

Synthesis of compound 225. Synthesis of compound 225 was completed as described above for compound 224 using butylamine in place of 1,2,3,4-tetrahydro-1-napthylamine. Analyzed by HPLC/MS. Calculated weight 375.56, Found 376.30 (M+H).

Synthesis of compound 226. Synthesis of compound 226 was completed as described above for compound 224 using phenethylamine in place of 1,2,3,4-tetrahydro-1-napthylamine. Analyzed by HPLC/MS. Calculated weight 423.60, Found 424.3 (M+H).

Synthesis of compound 227. Synthesis of compound 227 was completed as described above for compound 224 using cyclopentylamine in place of 1,2,3,4-tetrahydro-1-napthylamine. Analyzed by HPLC/MS. Calculated weight 387.57, Found 388.3 (M+H).

Synthesis of compound 228. Synthesis of compound 228 was completed as described above for compound 224 using tetrahydrofurfurylamine in place of 1,2,3,4-tetrahydro-1-napthylamine. Analyzed by HPLC/MS. Calculated weight 403.57, Found 404.3 (M+H).

Synthesis of compound 229. Synthesis of compound 229 was completed as described above for compound 224 using 4-chlorobenzylamine in place of 1,2,3,4-tetrahydro-1-napthylamine. Analyzed by HPLC/MS. Calculated weight 444.02, Found 444.2 (M+H).

Synthesis of compound 230. Synthesis of compound 230 was completed as described above for compound 224 using 4-bromomethylbenzoic acid in place of 3-bromomethylbenzoic acid. Analyzed by HPLC/MS. Calculated weight 449.64, Found 450 (M+H).

Synthesis of compound 231. Synthesis of compound 231 was completed as described above for compound 225 using 4-bromomethylbenzoic acid in place of 3-bromomethylbenzoic acid. Analyzed by HPLC/MS. Calculated weight 375.56, Found 376.30 (M+H).

Synthesis of compound 232. Synthesis of compound 232 was completed as described above for compound 226 using 4-bromomethylbenzoic acid in place of 3-bromomethylbenzoic acid. Analyzed by HPLC/MS. Calculated weight 423.60, Found 424.3 (M+H).

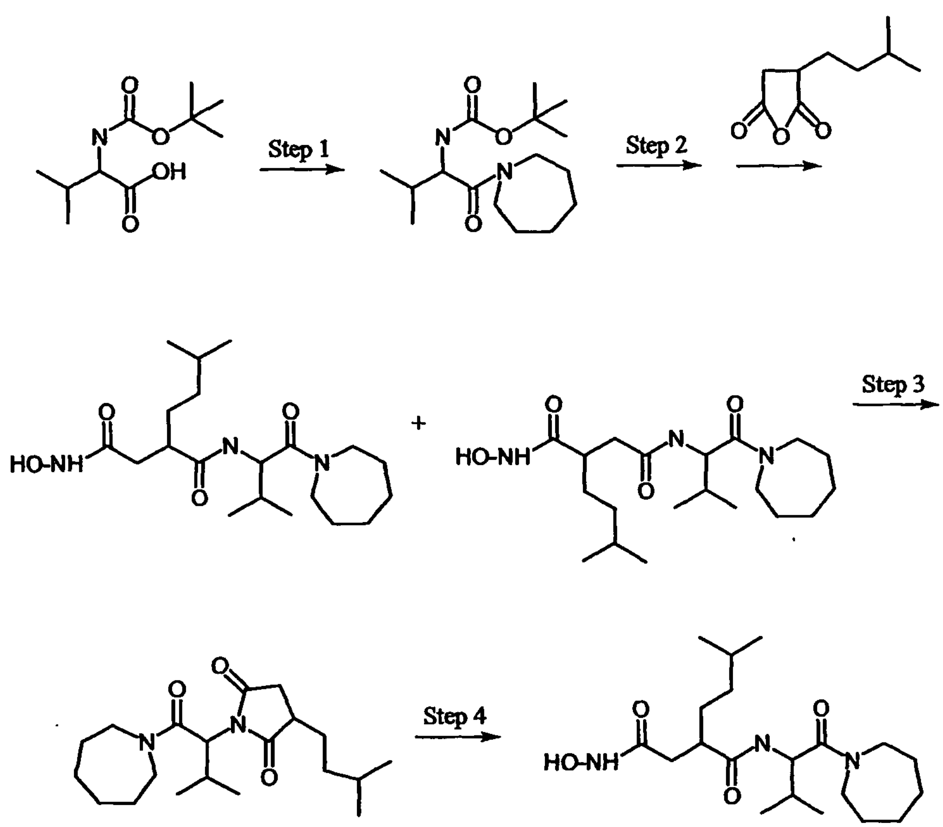
Synthesis of compound 233. Synthesis of compound 233 was completed as described above for compound 227 using 4-bromomethylbenzoic acid in place of 3-bromomethylbenzoic acid. Analyzed by HPLC/MS. Calculated weight 387.57, Found 388.3 (M+H).

Synthesis of compound 234. Synthesis of compound 234 was completed as described above for compound 228 using 4-bromomethylbenzoic acid in place of 3-bromomethylbenzoic acid. Analyzed by HPLC/MS. Calculated weight 403.57, Found 404.3 (M+H).

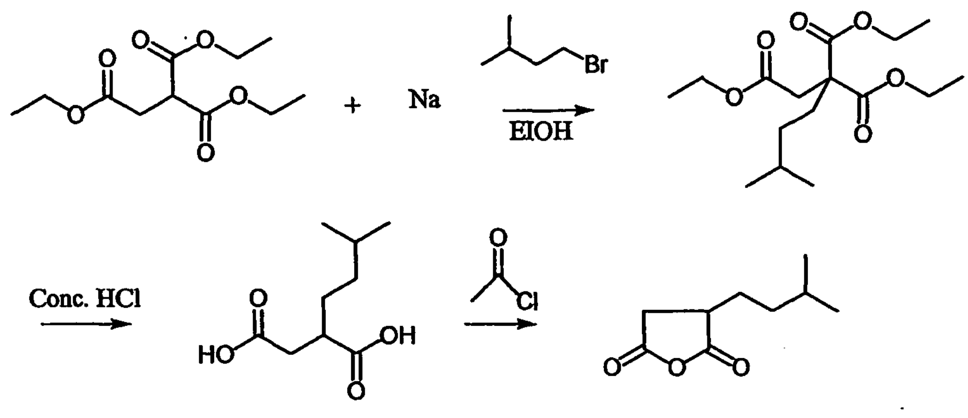
Synthesis of compound 235. Synthesis of compound 235 was completed as described above for compound 229 using 4-bromomethylbenzoic acid in place of 3-bromomethylbenzoic acid. Analyzed by HPLC/MS. Calculated weight 444.02, Found 444.2 (M+H).

5.6.1 Synthesis of Compounds of Formula XXI

Compounds represented by the following general structure are synthesized as described in section 5.6.1. See Scheme XXI for general synthetic scheme and Table 19 for representative R groups.



Scheme XX



Scheme XXII

Synthesis of compound 205

Synthesis of triethyl 5-methyl-1,2,2-hexanetricarboxylate. Sodium metal (467 mg , 20.3 mmol) was added to a stirred solution of triethyl 1,1,2-ethane tricarboxylate (5.0 g, 4.7 ml, 20.3 mmol) in ethanol (35 ml). After the metal had dissolved 1-bromo-3-methyl butane (3.1 g, 2.4 ml, 20.3 mmol) was added and the mixture was refluxed for 24 h. The mixture was cooled, filtered and resulting filtrate was concentrated. The residue was taken up in ether and washed with water. The water layer was back extracted with ether and the combine organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography using 10% EtOAc/hexanes to give 5.6 g (87%) of triethyl 5-methyl-1,2,2-hexanetricarboxylate as a colorless oil. The material was analyzed by ^1H NMR.

Synthesis of 3-carboxy-6-methyl heptanoic acid. Triethyl 5-methyl-1,2,2-hexanetricarboxylate (5.6 g, 17.7 mmol) was added to 55 ml conc. HCl and heated to reflux for 48 h. A white solid precipitate was noted. The reaction mixture was poured into ice and extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated to form a yellow oil. The oil crystallized upon standing to give 2.5 g (92%) of 3-carboxy-6-methyl heptanoic acid as a colorless crystalline solid which was analyzed by ^1H NMR.

Synthesis of isopentyl succinic anhydride. 3-Carboxy-6-methyl heptanoic acid (2.8 g,

14.9 mmol) was added to 5.2 ml acetyl chloride and heated to reflux for 3 h. Volatile material was removed in vacuo to give 2.5 g crude isopentyl succinic anhydride which was analyzed by ^{1}H NMR and used without further purification.

Synthesis of N-Boc-Valine homopiperidine amide. Homopiperidine (3.3 g, 33.2 mmol) was added to a solution of N-Boc-Valine (6.0 g, 27.7 mmol) and EDC (6.3 g, 33.2 mmol) in DCM (60 ml). The mixture was stirred for 16 h. The reaction mixture was diluted with DCM, washed with water, brine, dried ($MgSO_4$) and concentrated. Residue was purified by flash chromatography using 60% EtOAc in hexanes to give 3.4 g N-Boc-Valine homopiperidine amide as a colorless oil. This material analyzed by ^{1}H NMR.

Coupling of isopentyl succinic anhydride and isopentyl succinic anhydride to form 1. TFA (3 ml) was added to a solution of N-Boc-Valine (0.650 g, 2.2 mmol) homopiperidine amide in DCM (12 ml). The ice bath was removed and solution stirred for 4.5 h. Solvent was removed in vacuo and replaced with DCM (20 ml). 0.341 g (2.6 mmol) DIEA was added to the solution followed by addition of isopentyl succinic anhydride (0.442 g, 2.6 mmol). The solution was stirred for 72 h. The mixture was diluted with DCM, washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using EtOAc. 0.740 g (91%) of product 1 was obtained as a colorless oil which was analyzed by ^{1}H NMR.

Synthesis of compound 205. Coupling product 1 (0.740 g, 2.0 mmol) from the previous reaction was added to 0.71 ml acetyl chloride and heated to reflux for 3 h. EtOAc was added and washed with saturated $NaHCO_3$ (x2), brine, dried ($MgSO_4$) and concentrated. A cold solution of 0.264 g (3.8 mmol) hydroxamic acid hydrochloride salt in MeOH was treated with a solution of 0.319 g (5.7 mmol) KOH and let stand for 15 min at 0°C. The resulting solution was filtered, added to the residue from the previous step and stirred at room temperature for 48 h. The pH of the solution was neutralized to pH ~ 6 by addition of Dowex 50W-X8 resin.. The solution was filtered and concentrated. The residue was purified by flash chromatography using 80% EtOAc in hexanes. Material was analyzed by ^{1}H NMR and HPLC/MS. Calculated weight 383.25, Found 349.2, 382.3, 406.2 (M-NHOH, M+H, M+Na).

Synthesis of compound 206. Synthesis of compound 206 was completed as described above using bromomethyl cyclohexane in place of 1-bromo-3-methyl butane.

Synthesis of compound 207. Synthesis of compound 207 was completed as described above using 1-bromo-trans-2-butene in place of 1-bromo-3-methyl butane.

Synthesis of compound 208. Synthesis of compound 208 was completed as described above using 1-bromobutane in place of 1-bromo-3-methyl butane.

Synthesis of compound 209. Synthesis of compound 209 was completed as described above using benzyl bromide in place of 1-bromo-3-methyl butane.

Synthesis of compound 274. Boc-Val-OSu (0.5000 g, 1.59 mmol) was added to a solution of H-Nle-OMe.HCL (0.318 g, 1.75 mmol) in DCM (5 ml). DIEA (0.410 g, 0.553 ml, 3.18 mmol) was added and the reaction was agitated overnight. The reaction was diluted with DCM, washed with 5% citric acid, 5% K_2CO_3 and brine. The organic layers were dried over Na_2SO_4 and the solvent removed in vacuo. The residue was treated with 4.0 M HCl/dioxane and again the solvent was removed in vacuo.

The resulting amine was dissolved in DCM (2 ml). DIEA (0.172 g, 0.232 ml, 4.02 mmol) was added followed by the addition of benzoyl chloride (0.198 g, 0.164 ml, 1.41 mmol). The reaction was stirred overnight. The reaction was diluted with ether, washed with 5% citric acid, 5% K_2CO_3 and brine. The organic layers were dried over Na_2SO_4, and the solvent removed in vacuo. The residue was purified via flash chromatography to give the methyl ester. The ester was taken up in a basic solution of hydroxyl amine (1.0 M hydroxylamine; 0.5 M KOH) in MeOH. This was stirred for 15min and saturated $NaHCO_3$ was added to quench the reaction. The solution was extracted 3 X DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed in vacuo. The residue was purified via flash chromatography to give 0.054 g compound 274 which was analyzed by HPLC/MS. Calculated weight 349.43, Found 348.4 (M-H).

Synthesis of compound 275. Synthesis of compound 275 was completed as described above for compound 274 using D-Boc-Val-OSu in place of Boc-Val-OSu. Analyzed by HPLC/MS. Calculated weight 349.43, Found 348.4 (M-H).

Synthesis of compound 276. Synthesis of compound 276 was completed as described above for compound 274 using H-Cha-Ome.HCl in place of H-Nle-OMe.HCl. Analyzed by HPLC/MS. Calculated weight 389.50, Found 388.2 (M-H).

5.8.1 Synthesis of Hydantoin Derivatives

Compounds represented by Formulas XIX and XX are synthesized as described in section 5.8.1. See scheme XXIII for a general synthetic scheme and Tables 15-16 for representative structures.

Synthesis of compound 262.

Step 1:

D,L-Leucine (6.6 g, 0.050 mol) and KOCN (4.9 g, 0.060 mol) were allowed to react in 30 ml of water and 25 ml of pyridine for 30 min at 60°C. The solution mixture was cooled to room temperature then extracted with EtOAc (2 X 150 ml). 6N HCl (30 ml) and acetic acid (30 ml) was added to the aqueous phase and the mixture was heated to reflux for another 30 min. Upon cooling to room temperature, white solid precipitate out from solution. The solid was collected by vacuum filtration and washed repeatedly with water and ether. Yield 6.56 g, 84% of desired product. Analyzed by NMR. ^{1}H NMR (300 MHz, DMSO- d6) δ: 0.89 (dd, 6H), 1.38-1.49 (m, 2H), 1.76 (m, 1H), 4.00 (dd, 1H), 8.02 (s, 1H), 10.60 (s, 1H).

Step 2:

A mixture of isobutylhydantoin (468 mg, 3 mmol), benzyl bromide (392 ml, 3.3 mmol) and K_2CO_3 (622 mg, 4.5 mmol) in 7 ml of acetone were heated at 50°C overnight. EtOAc (15 ml) was added to the resulting mixture and washed with water then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude product was triturated with 40% DCM/hexane to give 420 mg of white solid as product. Yield 57%. Analyzed by NMR. ^{1}H NMR (300 MHz, CDCl3) δ: 0.99 (dd, 6H), 1.53 (m, 1H), 1.65 (m, 2H), 4.00 (dd, 1H), 4.68 (s, 2H), 6.02 (bs, 1H), 7.29-7.42 (m, 5H).

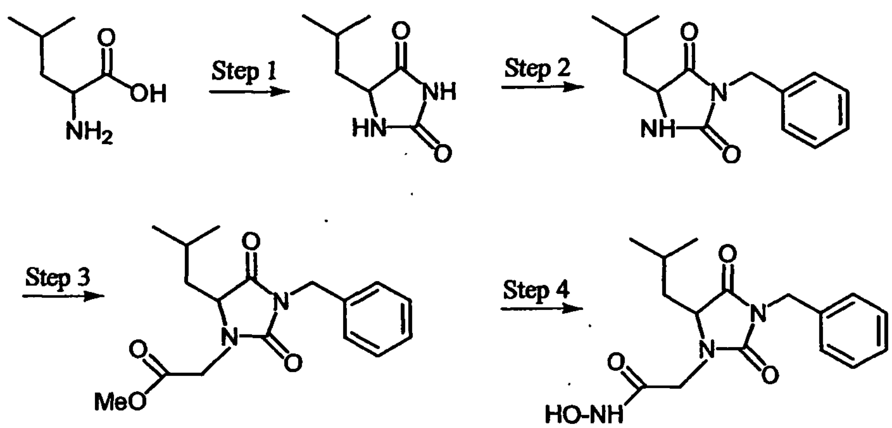
Step 3:

A mixture of isobutyl-benzyl-hydantoin (246 mg, 1 mmol), methylbromoacetate (114 ml, 1.2 mmol) and K_2CO_3 (207 mg 1.5 mmol) in 3 ml of acetone were heated in a seal tube at 50°C overnight. EtOAc (10 ml) was added to the resulting mixture and washed with water then brine. The organic phase was dried over anhydrous sodium sulfate and concentrated to dryness. The crude oil was carried to next step without further purification.

Step 4:

A methanolic solution of $NH_2OH.HCl$ (2.78 g in 34 ml) was cooled to 0°C. A methanolic solution of NaOH (3 g in 6 ml) was added, the mixture was stirred for 30 min and filtered. An aliquot (1 ml, 1.0 mmol NH_2OH) of this solution was added to a vial containing hydantoin methyl ester product (83 mg, 0.26 mmol) of the previous reaction.

The vial was shaken for 15 min then acidified to pH=5-6 with Dowex H+ resin.. The solution was then filtered and concentrated to dryness. The crude material was purified by flash chromatography using 5% MeOH/DCM. Analyzed by HPLC/MS. Calculated molecular weight 319.36. Found 320.1 (M+H).



Scheme XXIII

Synthesis of compound 261. Synthesis of compound 261 was completed as described above for compound 262 using D,L-Val in place of D,L-Leu. Calculated molecular weight 305.33. Found 306.1 (M+H).

Synthesis of compound 263. Synthesis of compound 263 was completed as described above for compound 262 using D,L-Phe in place of D,L-Leu. Calculated molecular weight 353.38. Found 354.1 (M+H).

Synthesis of compound 256. Synthesis of compound 256 was completed as described above for compound 262 using D,L-Nle in place of D,L-Leu. Analyzed by NMR. ^{1}H NMR (300 MHz, CD3OD) δ: 0.88 (t, 3H), 1.06 (m, 1H), 1.29 (m, 3H), 1.88 (m, 2H), 3.79 (m, 1H), 4.25 (m, 2H), 4.70 (m, 2H), 7.35 (m, 5H).

Synthesis of compound 255. Synthesis of compound 255 was completed as described above for compound 262 using D,L-Val in place of D,L-Leu and iodomethane in place of benzyl bromide. Analyzed by NMR. ^{1}H NMR (300 MHz, CD3OD) ^{1}H NMR (300 MHz, CD3OD) δ: 0.98 (dd, 6H), 2.27 (m, 1H), 3.00 (s, 3H), 4.04 (d, 1H), 4.03 (dd, 2H).

Synthesis of compound 258. Synthesis of compound 258 was completed as described

above for compound 262 using iodomethane in place of benzyl bromide. Analyzed by NMR. ^{1}H NMR (300 MHz, CD3OD) δ: 0.97 (dd, 6H), 1.73 (m, 2H), 1.90 (m, 1H), 3.00 (s, 3H), 4.05 (dd, 2H), 4.16 (dd, 1H).

Synthesis of compound 260. Synthesis of compound 260 was completed as described above for compound 262 using D,L-Nle in place of D,L-Leu and iodomethane in place of benzyl bromide. Calculated molecular weight 243.26. Found 244 (M+H).

Synthesis of compound 257. Synthesis of compound 257 was completed as described above for compound 262 using D,L-Met in place of D,L-Leu and iodomethane in place of benzyl bromide. Analyzed by HPLC/MS. Calculated molecular weight 261.30. Found 262 (M+H).

Synthesis of compound 259. Synthesis of compound 259 was completed as described above for compound 262 using D,L-Phe in place of D,L-Leu and iodomethane in place of benzyl bromide. Analyzed by HPLC/MS. Calculated molecular weight 277.28. Found 278.1 (M+H).

Synthesis of compound 300 (Scheme XXIV)

<u>Step 1:</u>

Chlorotrimethylsilane (274 ml, 2.17 mmol) was added to a stirring solution of D,L-Phenylalanine (358 mg, 2.17 mmol) and triethylamine (302 ml, 2.17 mmol) in anhydrous DCM (6 ml). The resulting mixture was allowed to stir for 15 min then ethyl 2-isocyanato-4-(methylthio)butyrate (400 mg, 1.97 mmol) was added. After stirring for 18 h, 100 ml of TFA was added and allowed to stir for additional 30 min then evaporated to dryness. The residue was taken in EtOAc (6 ml) and extracted with 1N HCl (2 X 3 ml) then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent removed under reduced pressure. The crude product was carried on to next step without further purification.

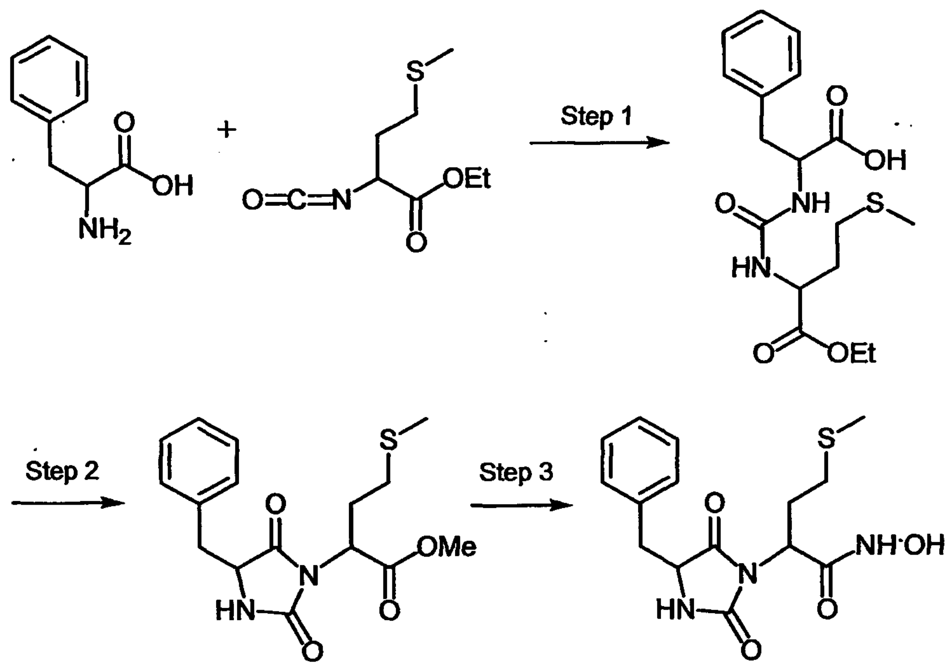
<u>Step 2:</u>

A mixture of acid (830 mg, 2.25 mmol) obtained from step 1 and 1,1'-carbonyldiimidazole (504 mg, 3.11 mmol) in 10 ml of anhydrous THF was allowed to stir at room temperature overnight. EtOAc (15 ml) was added to the mixture and washed with 1N HCl (10 ml), saturated aqueous $NaHCO_3$ (10 ml), and brine. The organic phase was dried over anhydrous sodium sulfate and concentrated to dryness. The crude product

was purified by flash chromatography using 25% EtOAc/Hexane as eluting solvent.

Step 3:

A methanolic solution of $NH_2OH.HCl$ (2.78 g in 34 ml) was cooled to 0°C. A methanolic solution of NaOH (3 g in 6 ml) was added, the mixture was stirred for 30 min and filtered. An aliquot (1 ml, 1.0 mmol NH_2OH) of this solution was added to a vial containing hydantoin methyl ester product (57 mg, 0.16 mmol) of the previous reaction. The vial was shaken for 30 min then acidified to pH 5-6 with Dowex H+ resin. The solution was then filtered and concentrated to dryness. The crude material was purified by flash chromatography using 5% MeOH/DCM. Analyzed by HPLC/MS. Calculated molecular weight 337.40. Found 336.1 (M-H).



Scheme XXIV

Synthesis of compound 246. Synthesis of compound 246 was completed as described above for compound 300 using D,L-Val in place of D,L-Phe. Analyzed by HPLC/MS. Calculated molecular weight 289.36. Found 288.1 (M-H).

Synthesis of compound 244. Synthesis of compound 244 was completed as described above for compound 300 using D,L-Leu in place of D,L-Phe. Analyzed by HPLC/MS. Calculated molecular weight 303.38. Found 302.1 (M-H).

Synthesis of compound 248. Synthesis of compound 248 was completed as described above for compound 300 using D,L-Nle in place of D,L-Phe. Analyzed by HPLC/MS. Calculated molecular weight 303.38. Found 302.1 (M-H).

Synthesis of compound 245. Synthesis of compound 245 was completed as described above for compound 300 using D,L-Met in place of D,L-Phe. Analyzed by HPLC/MS. Calculated molecular weight 321.42. Found 320.05 (M-H).

Synthesis of compound 253. Synthesis of compound 253 was completed as described above for compound 300 using ethyl 2-isocyanato-4-methylvalerate in place of ethyl 2-isocyanato-4-(methylthio)butyrate. Analyzed by HPLC/MS. Calculated molecular weight 321.42. Found 320.05 (M-H).

Synthesis of compound 247. Synthesis of compound 247 was completed as described above for compound 300 using ethyl 2-isocyanato-3-phenylpropionate in place of ethyl 2-isocyanato-4-(methylthio)butyrate. Analyzed by HPLC/MS. Calculated molecular weight 321.42. Found 320.05 (M-H).

Synthesis of compound 252. Synthesis of compound 252 was completed as described above for compound 300 using D,L-Met in place of D,L-Phe and ethyl 2-isocyanato-4-methylvalerate in place of ethyl 2-isocyanato-4-(methylthio)butyrate. Analyzed by HPLC/MS. Calculated molecular weight 303.38. Found 302.1 (M-H).

Synthesis of compound 254. Synthesis of compound 254 was completed as described above for compound 300 using D,L-Nle in place of D,L-Phe and ethyl 2-isocyanato-4-methylvalerate in place of ethyl 2-isocyanato-4-(methylthio)butyrate. Analyzed by HPLC/MS. Calculated molecular weight 285.34. Found 284.1 (M-H).

Synthesis of compound 251. Synthesis of compound 251 was completed as described above for compound 300 using D,L-Val in place of D,L-Phe and ethyl 2-isocyanato-3-methylbutyrate in place of ethyl 2-isocyanato-4-(methylthio)butyrate. Analyzed by HPLC/MS. Calculated molecular weight 257.29. Found 256.1 (M-H).

Synthesis of compound 301 (Scheme XXV)

Step 1:

EDC (1.03 g, 5.39 mmol) was added to a solution of Boc-Val (1.17 g, 5.39 mmol) in 8 ml of DCM and stirred for 30 min. At which time, pyrrolidine (0.45 ml, 7.42 mmol) was added and allowed the resulting mixture to stir for 18 h. After evaporation of solvent, the residue was taken up in EtOAc (10 ml) and extracted with 1N HCl (5 ml), saturated aqueous $NaHCO_3$ (5 ml) then brine (5 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude Boc amide.

Steps 2 and 3:

Boc amide (0.9 g, 3.3 mmol) was treated with 9 ml of 20% TFA in DCM for 3 h. The volatile material W-S removed b vacuum to give the TFA salt of the amino amide. To a solution of amino amide TFA salt (0.84 g, 2.9 mmol) and triethylamine (835 ml, 5.8 mmol) in 4 ml anhydrous DCM was added 2-isocyanato-4-methylvalerate (447 ml, 2.4 mmol) and stirred at room temperature overnight. After removal of volatile material, the residue was taken up in EtOAc (10 ml) and washed with 0.5N HCl (5 ml), water then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude was purified by flash chromatography using 75% EtOAc/hexane as eluting solvent. Analyzed by HPLC/MS. Calculated weight 355.48. Found 356.20 (M+H).

Step 4:

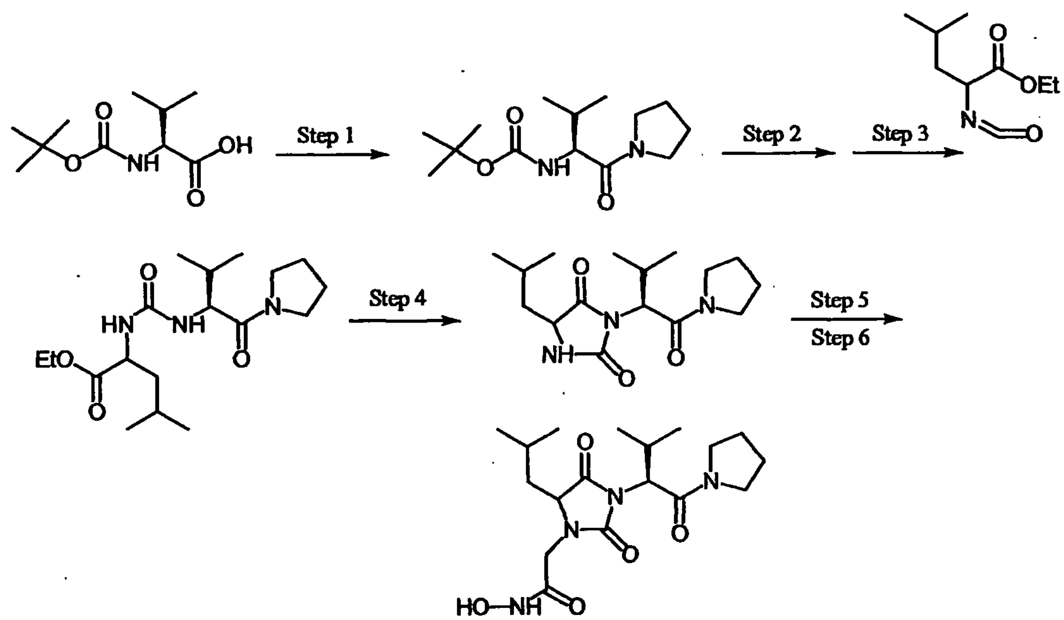
0.5 N NaOMe (1 ml, in MeOH) was added to a vial containing urea (0.17 g, 0.5 mmol) obtained from previous step. The mixture was allowed to shake for 6 h then acidified to pH 5-6 with Dowex H+ resin. The solution was then filtered and concentrated to dryness. The crude material was purified by flash chromatography using 75% EtOAc/hexane. Analyzed by NMR. ^{1}H NMR (300 MHz, CDCl3) δ: 0.96-1.10 (m, 12H), 1.59 (m, 1H), 1.82-2.06 (m, 6H), 3.15 (m, 1H), 3.56 (t, 4H), 4.12 (d, 1H), 4.39 (d, 1H), 6.70 (d, 1H).

Step 5:

A mixture of hydantoin (126 mg, 0.41 mmol), methylbromoacetate (154 ml, 1.6 mmol) and K_2CO_3 (113 mg 0.82 mmol) in 4 ml of acetone were heated at 60°C for 24 h. After evaporation of solvent, EtOAc (15 ml) was added to the residue and washed with water then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude material was purified by flash chromatography using 50% EtOAc/hexane.

Step 6:

A methanolic solution of $NH_2OH.HCl$ (2.78 g in 34 ml) was cooled to 0°C. A methanolic solution of NaOH (3 g in 6 ml) was added, the mixture was stirred for 30 min and filtered. An aliquot (0.4 ml, 0.4 mmol NH_2OH) of this solution was added to a vial containing hydantoin methyl ester product (24 mg, 0.06 mmol) of the previous reaction. The vial was shaken for 15 min then acidified to pH 5-6 with Dowex H+ resin.. The solution was then filtered and concentrated to dryness. The crude material was purified by flash chromatography using 5% MeOH/DCM. Analyzed by HPLC/MS. Calculated molecular weight 382.46. Found 381.2 (M-H).



Scheme XXV

Synthesis of compound 266. Synthesis of compound 266 was completed as described above for compound 301 using Boc-Gly in place of Boc-Val. Analyzed by HPLC/MS. Calculated molecular weight 340.38. Found 339.15 (M-H).

Synthesis of compound 267. Synthesis of compound 267 was completed as described above for compound 301 using Boc-Gly in place of Boc-Val and hexamethyleneimine in place of pyrrolidine. Analyzed by HPLC/MS. Calculated molecular weight 368.43. Found 367.2 (M-H).

Synthesis of compound 268. Synthesis of compound 268 was completed as described above for compound 301 using hexamethyleneimine in place of pyrrolidine. Analyzed by HPLC/MS. Calculated molecular weight 410.51. Found 409.20 (M-H).

Synthesis of compound 269. Synthesis of compound 269 was completed as described above for compound 301 using 2-isocyanato-3-propylbutyrate in place of 2-isocyanato-4-methylvalerate. Analyzed by HPLC/MS. Calculated molecular weight 410.51. Found 409.20 (M-H).

Synthesis of compound 272 (Scheme XXVI)

Step 1:

A mixture of Boc-Phe-Osu (1.09 g, 2.8 mmol) and R-(-)-Prolinol (0.5 g, 4.9 mmol) was stirred in 5 ml THF for 18 h.. After evaporation of solvent, the residue was taken up in EtOAc (10 ml) and extracted with 1N HCl (5 ml), saturated aqueous $NaHCO_3$ (5 ml) then brine (5 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude Boc amide.

Steps 2 and 3:

Same as step 2 and step 3 in the synthesis of compound 301.

Step 4:

Same as step 4 in the synthesis of compound 301.

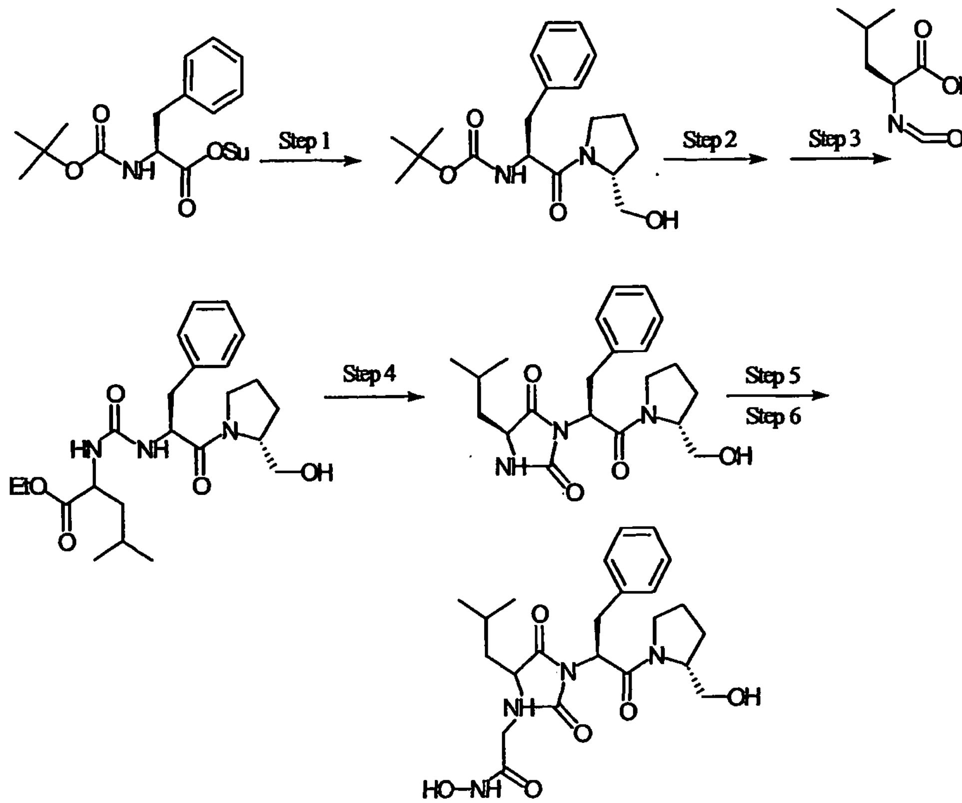
Step 5:

1M NaHMDS (139 ml, 0.14 mmol) was added to a solution of hydantoin (47.3 mg, 0.14 mmol) in 1 ml of THF at -78°C. The solution was allowed to warm to 0°C then added chlorotrimethysilane (17.6 ml, 0.14 mmol). After stirring for 15 min, another equivalent of NaHMDS (139 ml, 0.14 mmol) was added at 0°C followed by the addition of methylbromoacetate (19.7 ml, 0.21 mmol). The resulting mixture was allowed to warm to room temperature and stir for overnight. After evaporation of solvent, EtOAc (10 ml) was added to the residue and washed with water then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude material was purified by flash chromatography using 75% EtOAc/hexane.

Step 6:

Same as step 6 in the synthesis of compound 301.

Analyzed by HPLC/MS. Calculated molecular weight 460.53. Found 461.2 (M+H).



Scheme XXVI

Synthesis of compound 273. Synthesis of compound 273 was completed as described above for compound 272 using Boc-D-Phe-OSu in place of Boc-Phe-OSu. Analyzed by HPLC/MS. Calculated molecular weight 460.53. Found 461.2 (M+H).

Synthesis of compound 270. Synthesis of compound 270 was completed as described above for compound 272 using Boc-Gly-OSu in place of Boc-Phe-OSu. Analyzed by HPLC/MS. Calculated molecular weight 370.41. Found 371 (M+H).

Synthesis of compound 271. Synthesis of compound 271 was completed as described above for compound 272 using Boc-Val-OSu in place of Boc-Phe-OSu. Analyzed by HPLC/MS. Calculated molecular weight 412.49. Found 413 (M+H).

Synthesis of compound 264 (Scheme XXVII)

Step 1:

t-Butyl bromoacetate (1.34 ml, 9.1 mmol) was added to a suspension solution of L-Leucine-methylester (3.3 g, 18.1 mmol) and triethylamine (2.52 ml, 18.1 mmol) in 40 ml DMF and stirred for 18 h. The resulting mixture was poured into 40 ml of saturated aqueous ammonium chloride and extracted with ether (2 X 50 ml). The combined ethereal layers were dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude material was purified by flash chromatography using 20% EtOAc/hexane. Yield 2.3 g, 98%. Analyzed by NMR. ^{1}H NMR (300 MHz, CDCl3) δ: 1.00 (d, 6H), 1.53 (s, 9H), 1.58 (m, 2H), 1.82 (m, 1H), 3.32-3.40 (m, 3H), 3.78 (s, 3H).

Step 2:

A mixture of amine (1.6 g, 6.20 mmol) and methyl-3-isocyanato benzoate (1 g, 5.64 mmol) was stirred in 10 ml of DCM for 18 h. After removal of volatile material, the residue was taken up in EtOAc (30 ml) and washed with 1 N HCl (15 ml) then brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude material was carried to next step without purification.

Step 3:

Triethylamine (0.8 ml, 5.7 mmol) was added to a solution of urea (2.4 g, 5.64 mmol) obtained from previous step and heated to reflux in 10 ml of THF for 14 h. Volatile material was then removed in vacuo and the residue was purified by flash chromatography using 30% EtOAc/Hexane. Analyzed by NMR. ^{1}H NMR (300 MHz, CDCl3) δ: 1.05 (dd, 6H), 1.57 (s, 9H), 1.82-2.03 (m, 3H), 3.80 (d, 1H), 4.00 (s, 3H), 4.44 (dd, 1H), 4.65 (d, 1H), 7.64 (t, 1H), 7.73 (d, 1H), 8.11 (d, 1H), 8.17 (s, 1H).

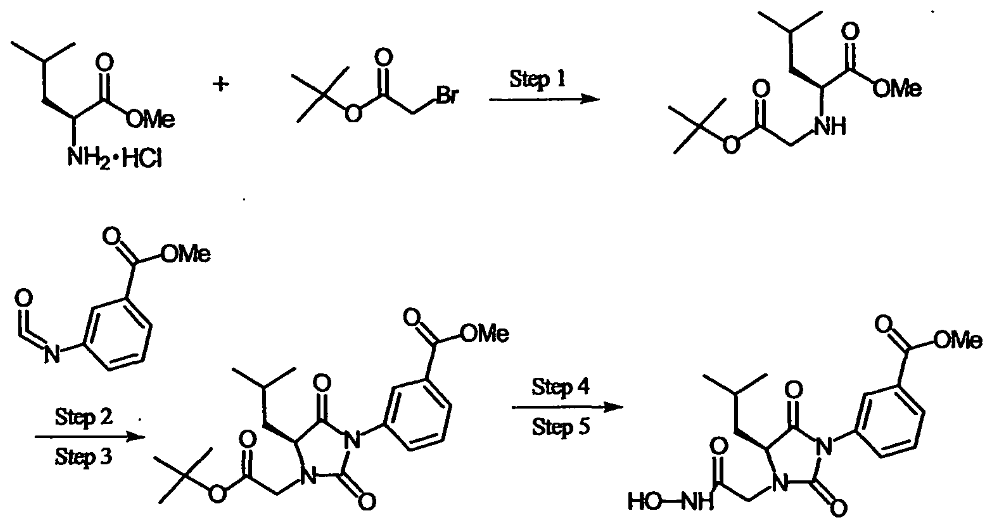
Step 4:

Hydantoin (0.2 g, 0.5 mmol) was treated with 50% TFA/DCM (3 ml) for 16 h. The volatile material was removed in vacuo to yield acid as crude product. Analyzed by NMR. ^{1}H NMR (300 MHz, CDCl3) δ: 1.05 (dd, 6H), 1.92-2.03 (m, 3H), 3.94 (d, 1H), 4.00 (s, 3H), 4.44 (dd, 1H), 4.73 (d, 1H), 7.64 (t, 1H), 7.73 (d, 1H), 8.15 (d, 1H), 8.19 (s, 1H).

Step 5:

EDC (100 mg, 1.04 mmol) and HOBT (70 mg, 1.04 mmol) was added to a solution of acid (180 mg, 0.52 mmol) in DMF (3 ml) and stirred for 1 h. O-Trimethylsilylhydroxylamine (90 ml, 1.04 mmol) was then added and the solution was stirred for 16 h. Saturated ammonium chloride solution was added and the mixture was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude material was purified by flash chromatography using 5% MeOH/DCM.

Analyzed by HPLC/MS. Calculated molecular weight 363.37. Found 362.10 (M-H).



Scheme XXVII

Synthesis of compound 265. Synthesis of compound 265 was completed as described above for compound 264 using 3-acetylphenylisocyanate in place of methyl-3-isocyanato benzoate. Analyzed by HPLC/MS. Calculated molecular weight 362.39. Found 4361.10 (M-H).

Synthesis of Compounds 310-311 (Scheme XXVIII)

Step 1:

Lithium diisopropylamide (3 ml, 6 mmol, 2M in hexane) was added to a solution of S-(+)- -trityloxymethyl- -butyrolactone (1.79 g, 5 mmol) in 15 ml THF at –78°C. After stirring for 30 min at –78°C, a solution of crotyl bromide (0.66 ml, 5.5 mmol) in 5 ml THF was added. The solution mixture was allowed to stir for 4 h at –78°C and then quenched with aqueous ammonium chloride (10 ml). After warming to room temperature, the resulting solution was extracted with EtOAc (2 X 30 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography (25% EtOAc/Hexane) to give desired product (1.7g, 84%). Analyzed by ^{1}H NMR (CDCl3) δ: 1.38 (m, 1H), 1.7 (m, 3H), 2.05-2.18 (m, 2H), 2.60 (m, 1H), 2.94 (m, 1H), 3.21 (dd, 1H), 3.48 (dd, 1H), 4.66 (m,1H), 5.43 (m, 1H), 5.62 (m, 1H), 7.24-7.63 (m, 15H).

Step 2:

A mixture of (S)- -buten-2-yl- -trityloxymethyl- -butyrolactone (1.7 g, 4.13 mmol), 10% Pd/C (228 mg) and EtOAc (80 ml) was hydrogenated at 45 psi for 3 h. The Pd catalyst was removed by filtration through a celite pad and washed with EtOAc (40 ml). The filtrate was concentrated to give 1.68 g (99%) of title compound. Analyzed by HPLC/MS. Calculated weight 414. Found 437 (M+Na).

Step 3:

Lithium diisopropylamide (2.43 ml, 4.86 mmol, 2 M in hexane) was added to a solution of (S)- -butyl- -trityloxymethyl- -butyrolactone (1.69 g, 4.05 mmol) in 20 ml THF at –78°C. After stirring for 1 h at –78°C, a solution of allyl bromide (0.45 ml, 5.26 mmol) in 2 ml THF was added. The solution mixture was allowed to stir for 4 h at –78°C and then quenched with aqueous ammonium chloride (10 ml). After warming to room temperature, the resulting solution was extracted with EtOAc (2 X 30 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. The crude residue was carried to next step without purification. Yield 1.8 g, quantitative. Analyzed by ^1H NMR (CDCl3) δ: 0.98 (t, 3H), 1.38 (m, 4H), 1.75(m, 2H), 2.05 (m, 2H), 2.42 (m, 2H), 3.25 (dd, 1H), 3.42 (dd, 1H), 4.60 (m, 1H), 5.23 (dd, 2H), 5.95 (m, 1H), 7.24-7.63 (m, 15H).

Step 4:

Trifluoroacetic acid (10 ml) was added to a solution of [S-(R*,R*)]- -butyl- -(propen-2-yl)- -trityloxymethyl- -butyrolactone (1.8 g, 3.96 mmol) in DCM (30 ml) at 0°C. The solution was stirred for 35 min at 0°C then concentrated to dryness. Saturated aqueous sodium chloride solution (30 ml) was poured into residue and extracted with DCM (2 x 20 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography (40% EtOAc/Hexane) to give 0.61 g (73%) of the desired product. Analyzed by HPLC/MS. Calculated weight 212.29. Found 213.15 (M+H).

Step 5 and 6:

A mixture of [S-(R*,R*)]- -butyl- -(propen-2-yl)- -hydroxymethyl- -butyrolactone (0.61 g, 2.88 mmol), NaOH (0.4 g, 10 mmol), THF (36 ml), and water (9 ml) was stirred vigorously for 21 h at room temperature. Additional NaOH (0.12 g, 3 mmol) was added after 20 h. The mixture was concentrated and the residue was taken up into MeOH (40 ml). A solution of sodium periodate (2.4 g, 11.2 mmol) and H_2O (6 ml) was added and the mixture was stirred for 16 h at room temperature. After concentration, the aqueous residue was acidified by 1N HCl and extracted with DCM (2 x 30 ml). The combined organic layers was dried over anhydrous sodium sulfate, filtered, and concentrated to give 550 mg of the title compound. Analyzed by HPLC/MS. Calculated weight 198.26. Found 197.4

(M-H).

Step 7:

NaOMe (6.7 ml, 0.5 M in MeOH) was added to a solution of L-valine pyrrolidine amide HCl salt (0.69 g, 3.33 mmol) in MeOH (5 ml). The resulting solution was then added to [S-(R*,R*)]- -butyl- -(propen-2-yl)- -hydroxy- -butyrolactone (0.55 g, 2.78 mmol) in MeOH (10 ml). Sodium cyanoborohydride (0.24 g, 3.75 mmol) was added and the solution was stirred for 16 h at room temperature. After concentration, saturated aqueous ammonium chloride solution was added to the residue and extracted with DCM (2 x 30 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to provide 0.96 g of the uncyclized intermediate as oil. Analyzed by HPLC/MS. Calculated weight 352.52. Found 351.40 (M-H).

Step 8:

The uncyclized intermediate (0.96 g, 2.73 mmol) in THF (5 ml) was added to a solution of carbonyldiimidazole (0.53 g, 3.27 mmol) in THF (15 ml) and stirred for 16 h at room temperature. After concentration, the residue was taken up in EtOAc (30 ml) and washed with 1N HCl (20 ml) and brine (20 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography (75% EtOAc/Hexane) to provide 0.53 g (58 % yield) of the title compound. Analyzed by HPLC/MS. Calculated weight 334.51. Found 335.40 (M+H).

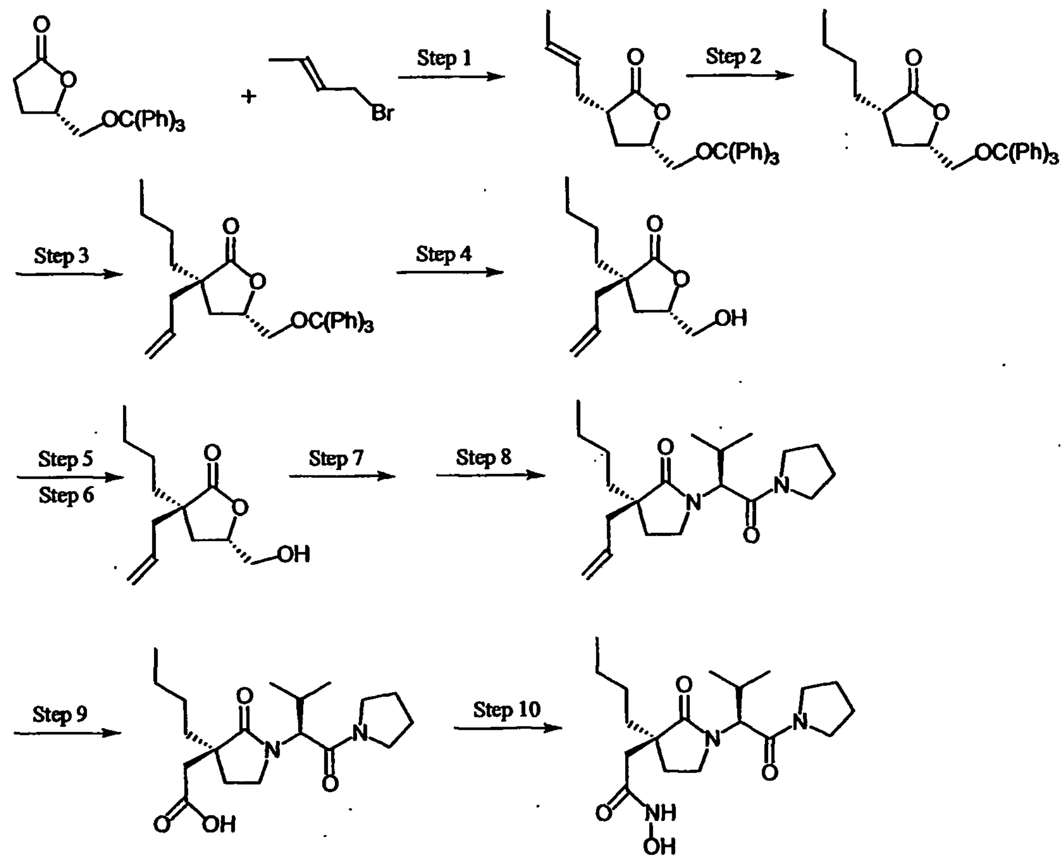
Step 9: **Synthesis of compound 310**

Ruthenium (IV) oxide hydrate (41 mg, 0.3 mmol) was added to a mixture of sodium periodate (2.55 g, 12 mmol), H_2O (33 ml), CH_3CN (33 ml) and CCl4 (33 ml). The mixture was stirred for 20 min at room temperature and then $NaHCO_3$ (3.15 g, 37.5 mmol) and H_2O (17 ml) were added. After stirring for additional 5 min, a solution of pyrrolidineacetamide (0.5 g, 1.5 mmol) in CH_3CN (12 ml) was added. After stirring for 10 min, the residue was poured into a mixture of H_2O (100 ml) and EtOAc (200 ml). The aqueous layer was removed and the organic layer was extracted with 10% aqueous Na_2CO_3 solution (2 x 20 ml). The combined basic layers were acidified with 6N HCl and extracted with DCM (3 x 70 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc) to provide 108 mg (20%) of compound 310. Analyzed by HPLC/MS. Calculated weight 352.48. Found 353.40 (M+H).

Step 10: **Synthesis of compound 311**

To a stirring solution of acid (50 mg, 0.14 mmol) and triethylamine (23 ml, 0.17 mmol) in THF (2 ml) was added isobutylchloroformate (20 ml, 0.16 mmol) at 0°C. After

stirring for 15 min at 0°C, $TMSONH_2$ (36 ml, 0.21 mmol) was added and allowed the resulting mixture to stir for additional 2 h at room temperature. EtOAc (5 ml) was added to the solution and extracted with saturated aqueous ammonium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was



Scheme XXVIII

purified by flash chromatography (10% MeOH/DCM) to provide 24 mg (50%) of compound 311. Analyzed by HPLC/MS. Calculated weight 367.49. Found 366.40 (M-H).

5.9.1 <u>Selectivity Profiles</u>

See section 4.9 for description of selectivity assays.

The selectivity of the inhibitors was calculated as the ratio of the IC50 for the compound versus thermolysin (THERM) divided by the IC50 for the compound versus peptide deformylase (Fe-PDF). The metalloproteases carboxypeptidase (CPEP), collagenase (COLL) and angiotensin converting enzyme (ACE) were also used in these

studies but the IC50 for thermolysin (THERM) was generally the smallest for these enzymes.

For Fe-PDF, inhibition is given as percent inhibition and for THERM, CPEP, COLL and ACE the inhibition values are the inhibition relative to controls with no inhibitor (enzymatic reaction without test compound divided by reaction with test compound).

Table 17

Selectivity Profiles

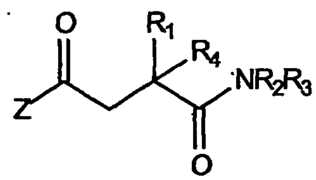
COMPOUND NUMBER	SELECTIVITY INDEX	Fe PDF	THERM	CPEP	Coll	ACE
10	30000	100	0.94	0.4	0.34	0.58
20	15000	100	1.11	0.06	0.15	0.11
28	30000	100	1.14	0.79	0.83	0.84
35	15000	100	0.98	0.52	0.47	0.01
42	30000	100	0.9	0.5	0.62	0.2
53	60000	100	1.04	0.15	0.28	0.19
62	30000	100	1.09	0.34	0.28	-0.16
64	30000	100	1.07	0.92	0.33	-0.45
65	10000	100	1.09	0.93	0.41	1.1
66	7500	100	1.1	0.96	0.26	0.81
86		100	0.35	0.28	0.32	0.12
89		100	0.27	0.74	0.25	-0.26
90	15000	100	0.82	0.81	0.53	0.75
97		100	0.39	0.75	0.47	0.53
99	15000	100	0.51	0.93	0.38	0.97
100	30000	100	0.42	0.79	0.67	0.79
109	10000	100	1.02	0.4	0.4	-0.05
111	10000	100	0.97	0.45	0.51	0.16
124	3750	100	0.91	0.8	0.77	0.78
72	15000	100	0.16	0.73	0.11	0.4
74	3750	100	1.07	0.93	0.37	1

COMPOUND NUMBER	SELECTIVITY INDEX	Fe PDF	THER M	CPEP	Coll	ACE
218	6000	100	0.88	0.39	0.51	0.6
219	15000	100	0.95	0.15	0.6	-0.31
221	10000	100	1.01	0.27	0.49	0.51
201	10000	100	0.82	0.64	0.7	1.11
193	15000	100	1.01	0.97	0.93	0.89
238	7500	100	0.83	0.58	0.91	0.99
143	1500	100	0.06	0.96	0.65	1.1
146	850	100	0.03	1.06	0.03	0.96
164	1667	100	0.88	0.62	0.97	1.53
214	30000	100	0.54	0.93	1	0.74
179	30000	100	0.59	0.96	0.82	0.28
193	30000	100	0.57	0.04	1.2	0.84
315	1000	100	0	0.99	0.65	0.95
316	167	102.5	0.01	0.95	0.8	1.02
241	47	100	0.97	1	0.89	0.69
274	15000	100	1.02	1.14	1.01	1
277	2727	100	0.84	0.94	1.07	0.72
279	189	100	0.95	1.03	1.03	1.15
234	166	104.1	0.99	0.96	1	0.97
311	1667	100	0.91	1.1	1.02	1.94

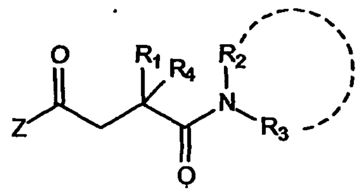
THE CLAIMS

We Claim:

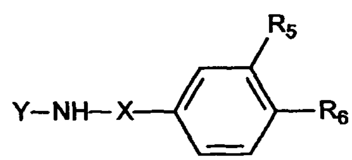
1. A compound represented by Formulas I- IV:



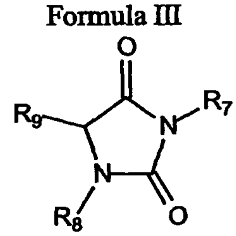
Formula I



Formula II



Formula III



Formula IV

including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein:

Z is NHOH or OR_a wherein R_a is H, alkyl or a biocleavable moiety;

X is C=O or O=S=O;

Y is heteroalkyl, heterocyclic, or substituted derivatives thereof;

R_1 is C_1-C_{10} alkyl, cycloalkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof;

R_2 and R_3 together represent a 4, 5, 6, or 7 membered heterocyclic ring optionally substituted with one of the following substituents -OH, $-CH_2OH$, -O-C(=O)-heterocyclic, -O-C(=O)-NH-aryl, -NH-C(=O)-aryl, -C(=O)-N(C_2-C_6 alkyl)$_2$, -NH-(C_1-C_6 alkyl)-heterocyclic, -NH-C(=O)-NH-alkyl, -NH-C(=O)-NH-aryl, -NH-C(=O)-NH-heterocyclic; or

R_2 and R_4 together form a ring through a $-CH_2$-CH_2- linkage wherein R_3 is H, C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof; or R_2 is methyl;

R_3, as defined above forms a ring with R_2, or represents H, or is alkyl, heteroalkyl, aryl, heterocyclic, and substituted derivatives thereof;

R_3 when not in a ring with R_2 is alkyl, heteroalkyl, aryl, heterocyclic, and substituted derivatives thereof;

R_4 when not in a ring with R_2 is H, C_1-C_{10} alkyl, aryl, heterocyclic, heteroalkyl or a substituted derivative thereof; or is together with R_2 as defined above to form a ring through a $-CH_2$-CH_2- linkage;

R_5 is -H, $-NO_2$, $-NH_2$, -NH-C(=O)-H, -NH-C(=O)-CH_3, -NH-S(O_2)-CH_3), $-CH_2$-NH-alkyl, $-CH_2$-NH-heteroalkyl, $-CH_2$-NH-heterocycyl, or substituted derivatives thereof;

R_6 is -H, $-NO_2$, $-NH_2$, -NH-C(=O)-H, -NH-C(=O)-CH_3, -NH-S(O_2)-CH_3, $-CH_2$-NH-(alkyl), $-CH_2$-NH-heteroalkyl, $-CH_2$-NH-heterocycyl, or substituted derivatives thereof;

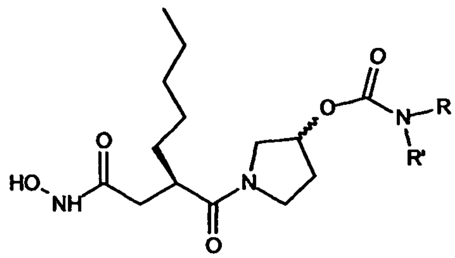
R_7 or R_8 is -CHR_{10}-C(=O)-NH-OH;

R_7 or R_8 when not -CHR-C(=O)-NH-OH is alkyl, heteroalkyl, heterocycyl, alkylaryl, alkylheterocyclic, or substituted derivatives thereof;

R_9 is H, alkyl, heteroalkyl, heterocycyl, alkylaryl, alkylheterocyclic, or substituted derivatives thereof; and,

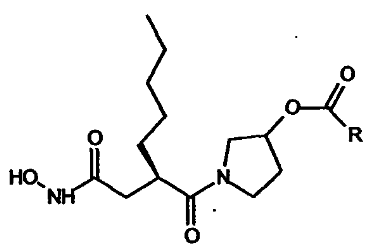
R_{10} is H, alkyl, heteroalkyl, heterocycyl, alkylaryl, alkylheterocyclic, or substituted derivatives thereof.

2. A compound of the formula:



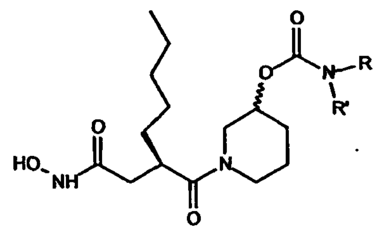
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R' is H, and R is selected from the from the group consisting of 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, phenyl, 4-methoxy-phenyl, 4-trifluoromethoxy-phenyl, 4-(N,N-Dimethyl-amino)-phenyl, 4-bromo-phenyl, 4-methyl-phenyl, 4-n-butyl-phenyl, 4-trifluoro-methyl-phenyl, 2-methoxy-phenyl, 2-ethyl-phenyl, 2-i-propyl-phenyl, 3-methyl-phenyl, 3-nitro-phenyl, 3-methyl-mercapto-phenyl, 4-chloro-3-nitro-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 2,4-dichloro-phenyl, 2,4-dimethoxy-phenyl, 4-chloro-2-tri-fluoromethyl-phenyl, 2,5-difluoro-phenyl, 2-methoxy-5-chloro-phenyl, 2-methoxy-5-methyl-phenyl, 3,5-dimethyl-phenyl, 3,5-bis-(tri-fluoromethyl)-phenyl, 3,5-dichloro-phenyl, 4-(2,6-dichloro-pyridyl), n-propyl, benzyl, 2-(ethyl-2-thiophene), 4-phenoxy-phenyl, 4-trifluoro-methanemercapto-phenyl, 2-phenyl-phenyl, and 2-phenoxy-phenyl.

3. A compound of the formula:



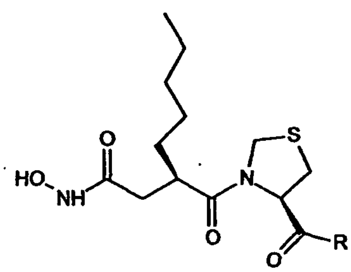
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the from the group consisting of N-pyrrolidine, N-pyrrolidine-2-methanol, N-piperidine, N-homo-piperidine, N-morpholine, and N-3S-pyrrolidinol.

4. A compound of the formula:



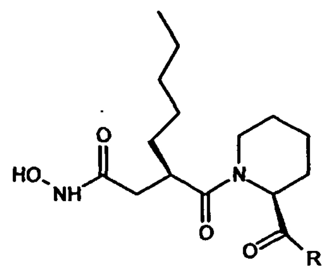
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of phenyl, 3,5-di-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 4-methoxy-phenyl, 4-(N,N-di-methylamino)-phenyl, 4-trifluoro-methoxy-phenyl, and 4-fluoro-phenyl, and R' is H.

5. A compound of the formula:



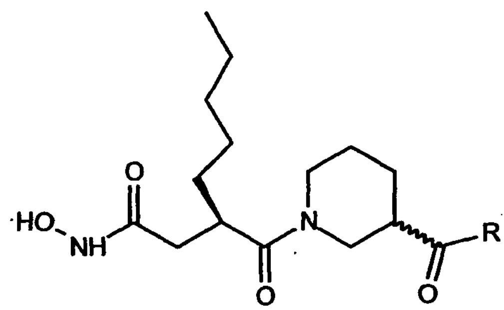
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof wherein R is selected from the group consisting of N-isobutylamine, N-cyclopentylamine, N-cyclohexylamine, N-tetrahydro-furfurylamine, N-furfurylamine, N-thiophenmethylamine, N-benzylamine, 2-aminothiazole, N-dimethylamine, N-pyrrolidine, N-piperidine, N-homopiperidine, N-morpholine, 2R,6S-dimethyl-morpholine, and N-thiomorpholine.

6. A compound of the formula:



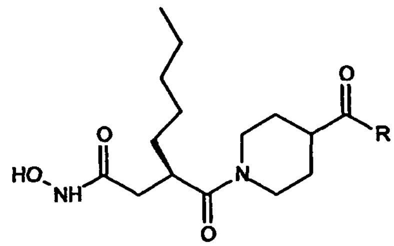
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of N-isobutylamine, N-cyclopentylamine, N-cyclohexylamine, N-tetrahydro-furfurylamine, N-furfurylamine, N-2-thiophenemethylamine, N-methyl-3-pyridyl, N-benzylamine, 2-aminothiazole, N-dimethylamine, N-piperidine, N-homo-piperidine, N-morpholine, N-2,6-dimethyl-morpholine, N-thiomorpholine, and N-Methyl-N-piperazine.

7. A compound of the formula:



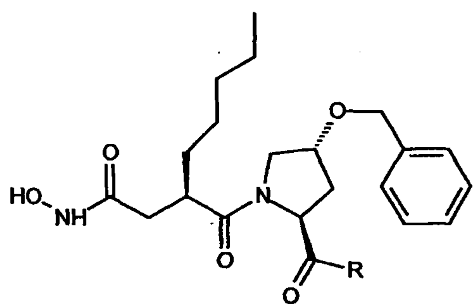
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of N-isobutylamine, N-cyclopentylamine , N-cyclohexylamine, N-tetrahydro-furfurylamine, N-furfurylamine, N-thiophene-methylamine, N-2-methylpyridyl, N-benzylamine, N-2-aminothiazole, N-dimethylamine, N-pyrrolidine, N-piperidine, N-homopiperidine, N-morpholine, N-2R,6S-dimethylmorpholine, N-thiomorpholine, and N-methyl-N-piperazine.

8. A compound of the formula:



including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R represents is selected from the group consisting of N-isobutylamine, N-cyclopentylamine, N-furfurylamine, N-thiophene-methylamine, N-2-methyl-2-pyridyl, N-benzyl, N-2-aminothiazole, N,N-dimethylamine, N-pyrrolidine, N-piperidine, N-homopiperidine, N-morpholine, 2,6-dimethyl-morpholine, and N-thiomorpholine.

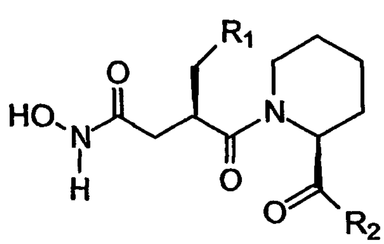
9. A compound of the formula:



including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of N-2-aminothiazole,

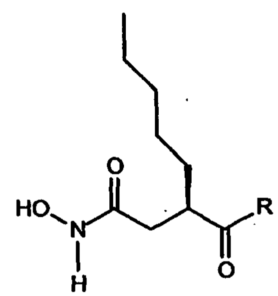
N-dimethylamine, N-2-methylpyridyl, N-cyclopentylamine, and N-thiomorpholine.

10. A compound of the formula:



including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of 3,4-difluorophenyl, phenyl and cyclohexyl; and R_2 is selected from the group consisting of N-2-aminothiazole and N-pyrrolidine.

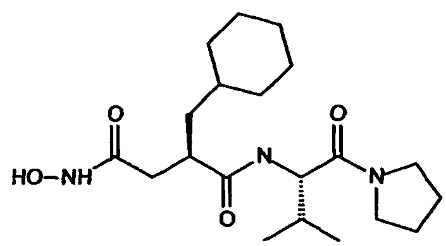
11. A compound of the formula:



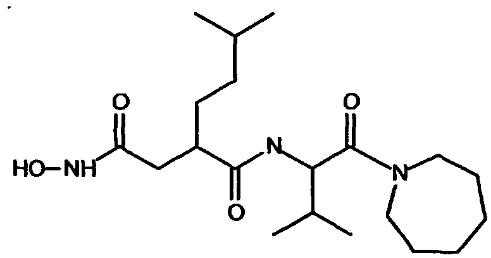
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of valinyl-pyrrolidinamide, amino-valeryl-N,N-dimethylamide, phenylalanyl-N,N-dimethylamide, methionyl-N,N-dimethylamide, O-benzyl-serinyl-N,N-dimethylamide, O-benzyl-tyrosinyl-N,N-dimethylamide, amino-valeryl pyrrolidinamide, phenylalanyl pyrrolidinamide, methionyl pyrollidinamide, O-benzyl-serinyl pyrollidinamide, O-benzyl-tyrosinyl pyrrolidinamide, valinyl-piperidinamide, amino-valeryl-piperidinamide, phenylalanyl piperidinamide, methionyl-piperidinamide, O-benzyl-serinyl piperidinamide, O-benzyl-tyrosinyl-piperidinamide, valinyl-benzylamide, amino-valeryl-benzylamide, phenylalanyl-benzylamide, methionyl-benzylamide, O-benzyl-tyrosinyl-benzylamide, O-benzyl-tyrosinyl-benzylamide, phenylalanyl anilinamide, N-butylamine, N-pentylamine, N-pyrrolidine, N-piperidine, N-furfurylamine, N-adamantylamine, N-aniline, N-[4-(N-morpholine)]-aniline, N-[4-pentamethyloxy]-aniline, N-(4-fluoro)-aniline, N-(3-bromo)-aniline, N-(4-bromo)-aniline, N-(4-chloro)-aniline, N-(3,5-dimethoxy)-aniline, N-(3-phenoxy)-aniline, N-(4-phenoxy)-aniline, N-(4-N-acetamidyl) aniline, N-serinyldimethyl amide, lysinyl-pyrrolidinamide, glycinyl-(2-acetohydroxamate)-pyrrolidiniamide, glycinyl-piperidinamide, lysinyl-dimethylamide, lysinyl-piperidinamide, glycinyl-benzyl amide, lysinyl-benzyl amide, glycinyl-4-methoxy-anilinamide, lysinyl-4-methoxy-anilinamide, glycinyl-(2-acetohydroxamate)- 4-methoxy anilinamide, glycinyl-(2-propiohydoxamate)-4-methoxy anilinamide, glycinyl-(4-fluoro)-anilinamide, N-propionate-(4-fluoro)-anilamide, N-2-

piperidinemethanol, N-4-piperidineethanol, (N-benzylethanolamine, N,N-diethanolamine, N-methyl-N-[(3,4-dimethoxy)-2-phenylethyl]-amine, N-2-(methylamino)ethanol, N-pyrrolidine-2-pyrrolidinamide, N-pyrrolidine-3-benzylamide, N-piperazine-N-pyrrolidinamide, N-piperazine-N-benzylamide, N-azetidine-3-benzylamide, 3-pyrrilidinol, 2-pyrrolidinol, 3-piperidinol, N-3-benzylamide-azetidine, N-piperidine-2-pyrrolidinamide and N-azetidine-(3-O-anilinamide).

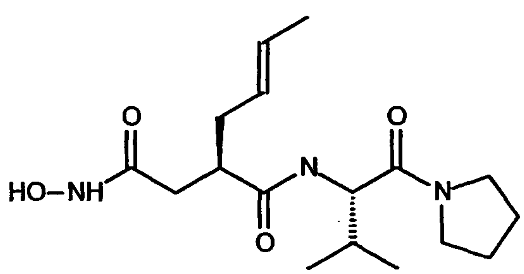
12. A compound of the formula:



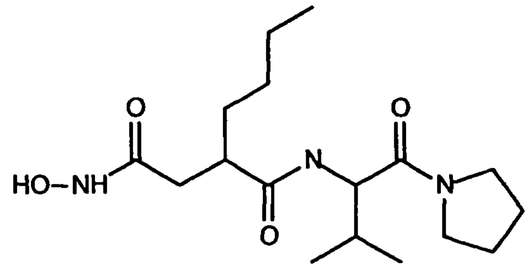
or



or

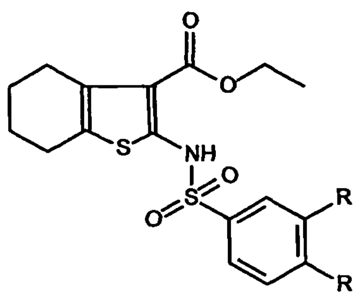


or



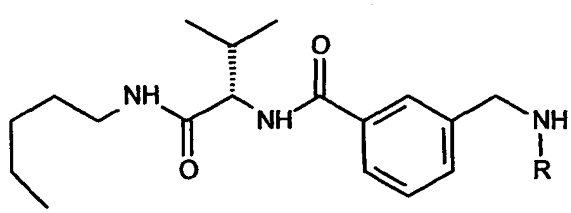
including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof.

13. A compound of the formula:



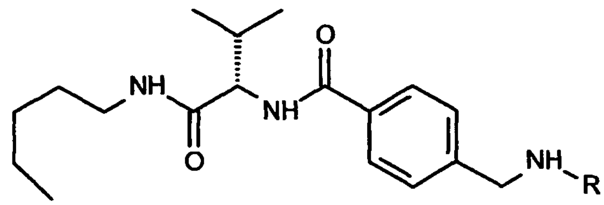
or a pharmaceutically acceptable salt thereof, wherein the R side chains are independently selected from the group consisting of H, NO_2, $NHC(=O)CH_3$, $NHC(=O)H$, and $NHS(O_2)CH_3$.

14. A compound of the formula:



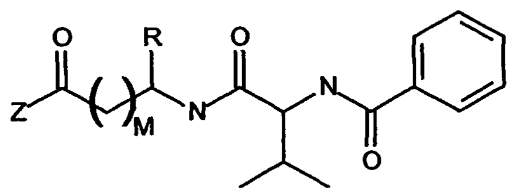
including enantiomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of 1-naphthalene 1,2,3,4-tetrahydride, n-butyl, ethyl 2-phenyl, cyclopentyl, 2-methyltetrahydrofuran,and 4-chlorophenyl.

15. A compound of the formula:



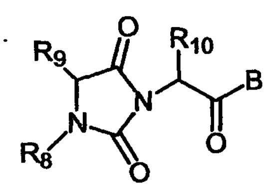
including enantiomers, and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of 1-naphthalene 1,2,3,4-tetrahydride, n-butyl, ethyl 2-phenyl, cyclopentyl, 2-methyltetrahydrofuran, and 4-chlorophenyl.

16. A compound of the formula:



including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof wherein z is selected from the group consisting of -OH and -NH-OH, M is 0 or 1; and R is selected from the group consisting of alkyl, aryl, alkylaryl, heterocycyl and substituted derivatives thereof.

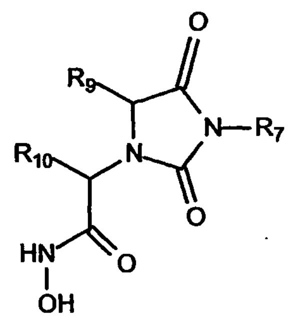
17. A compound of the formula:



including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof wherein B is selected from the group consisting of -NH-OH, N-isobutylamine, N-cyclopentylamine, N-furfurylamine, N-thiophene-methylamine, N-methyl-2-pyridine, N-benzyl, N-2-aminothiazole, N,N-dimethylamine, N-pyrrolidine, N-piperidine, N-homopiperidine, N-morpholine, N-2,6-dimethyl-morpholine, N-thiomorpholine, N-3-pyrrilidinol, N-2-pyrrolidinol, N-3-piperidinol, and N-2-

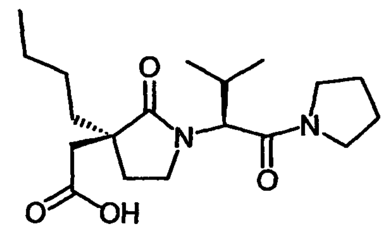
pyrrolidine-methanol; R_8 is selected from the group consisting of H,-CH_3, -$CH_2C(=O)NH$-OH, -$CH_2CH(CH_3)_2$,-$(CH_2)_3CH_3$, -$CH(CH_3)_2$,-$CH_2(C_6H_5)$,-$CH_2CH_2SCH_3$, alkyl, aryl, alkylaryl, heteroalkyl, heterocycyl, and substituted derivatives thereof; R_9 is selected from the group consisting of H,-CH_3, -$CH_2C(=O)NH$-OH, -$CH_2CH(CH_3)_2$,-$(CH_2)_3CH_3$, -$CH(CH_3)_2$,-$CH_2(C_6H_5)$,-$CH_2CH_2SCH_3$, alkyl, aryl, alkylaryl, heteroalkyl, heterocycyl and substituted derivatives thereof; and R_{10} is selected from the group consisting of H, -CH_3, -$CH_2C(=O)NH$-OH, -$CH_2CH(CH_3)_2$,-$(CH_2)_3CH_3$, -$CH(CH_3)_2$,-$CH_2(C_6H_5)$,-$CH_2CH_2SCH_3$, alkyl, aryl, alkylaryl, heteroalkyl, heterocycyl and substituted derivatives thereof.

18. A compound of the formula:

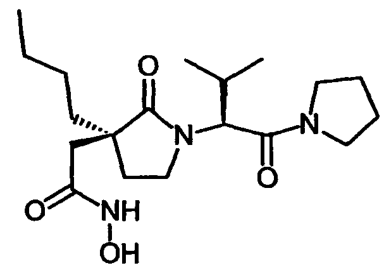


including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof wherein R_7 is selected from the group consisting of H,-CH_3, -$CH_2C(=O)NH$-OH, -$CH_2CH(CH_3)_2$,-$(CH_2)_3CH_3$, -$CH(CH_3)_2$,-$CH_2(C_6H_5)$,-$CH_2CH_2SCH_3$, alkyl, aryl, alkylaryl, heteroalkyl, heterocycyl, and substituted derivatives thereof; R_9 is selected from the group consisting of H,-CH_3, -$CH_2C(=O)NH$-OH, -$CH_2CH(CH_3)_2$, -$(CH_2)_3CH_3$, -$CH(CH_3)_2$,-$CH_2(C_6H_5)$,-$CH_2CH_2SCH_3$, alkyl, aryl, alkylaryl, heteroalkyl, heterocycyl and substituted derivatives thereof; and R_{10} is selected from the group consisting of H, -CH_3, -$CH_2C(=O)NH$-OH, -$CH_2CH(CH_3)_2$, -$(CH_2)_3CH_3$, -$CH(CH_3)_2$, -$CH_2(C_6H_5)$, -$CH_2CH_2SCH_3$, alkyl, aryl, alkylaryl, heteroalkyl, heterocycyl and substituted derivatives thereof.

19. A compound of the formula:



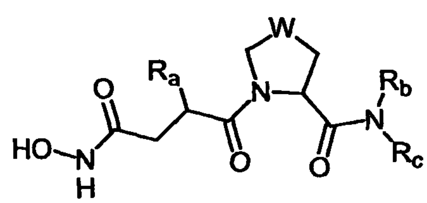
or



including all enantiomers, diastereomers and mixtures thereof, or a pharmaceutically acceptable salt thereof.

20. A compound represented by Formula XXIII:

including all enantiomers, diastereomers, and mixtures thereof, or a pharmaceutically acceptable salt thereof,



Formula XXIII

wherein

R_a is alkyl which may be substituted by aryl, halogenaryl, or cycloalkyl;

R_b and R_c may be the same or different and each represents hydrogen, alkyl, heterocyclyl-alkyl, aryl, aryl-alkyl, cycloalkyl, or heterocyclic ring which may be substituted by alkyl, or R_b and R_c together with nitrogen from 5, 6, or 7 membered heterocyclic ring which may contain another heteroatom selected from nitrogen, sulfur, or oxygen; and

W is selected from the group consisting of sulfur and ethylenyl.

21. The compound according to claim 20 having Formula XXIV: wherein R_b and R_c are the same as defined in claim 20.

22. The compound according to claim 20 having Formula XXV: wherein R_b and R_c are the same as defined in claim 20

23. The compound according to claim 20 having Formula XXVI: wherein R_a is selected from the group consisting of aryl, halogenoaryl, and cycloalkyl, and R_b and R_c are the same as defined in claim 20.

24. The compound according to claim 21, wherein R_b and R_c may be the same or different and each represents a hydrogen atom, isobutyl, methyl, cyclopentyl, cyclohexyl, tetrahydrofurfuryl, furfuryl, 2-thienylmethyl, benzyl, 2-thiazolyl, or R_b and R_c together with nitrogen form a heterocyclic ring which is selected from the group consisting of 1-pyrrolidinyl, piperidino, homopiperidino, morpholino, 2,6-dimethylmorpholino, and thiomorpholino.

25. The compound according to claim 22, wherein R_b and R_c may be the same or different and each a hydrogen atom, isobutyl, methyl, cyclopentyl, cyclohexyl, tetrahydrofurfuryl, furfuryl, 2-thienylmethyl, 3-pyridylmethyl, benzyl, 2-thiazolyl, or R_b and R_c together with nitrogen form a heterocyclic ring which is selected from the group consisting of piperidino, morpholino, 2,6-dimethylmorpholino, thiomorpholino, 4-methyl-1-piperazinyl, and 1-pyrrolidinyl.

26. The compound according to claim 23, wherein R_a is selected from the group consisting of 3,4-difluorophenyl, phenyl, and cyclohexyl, and R_b and R_c may be the same or different and each represents hydrogen or 2-thiazolyl or R_b and R_c together with nitrogen form 1-pyrrolidinyl.